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THE EFFECT OF BILE SALTS ON RECOVERY OF LIVER FUNCTION AFTER RELEASE OF COMMON DUCT OBSTRUCTION*

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THERE IS the impression in surgical and clinical medicine that the administration of bile salts, orally or intravenously, will increase the rate of elimination of bile pigments accumulated in the blood stream because of biliary obstruction or liver damage. A number of surgeons, such as Boyce[1, 2] and Finsterer[3] have used dehydrocholic acid intravenously in the postoperative management of patients in whom gall bladder or biliary tract surgery had been performed. They report an improvement in the general condition of the patients and a decrease in the intensity of the jaundice, as well as an increased "flushing out" effect of the biliary passages. However, they present no accurate studies on the rate of elimination of bile pigment, and one simply gets the impression that a decrease in jaundice occurred simultaneously with the use of bile salts. Appel and Jankelson[4, 5] used sodium dehydrocholate in arsenical hepatitis due to neoarsphenamine injections, and although their data and results are not decisive they conclude that recovery from jaundice and toxic hepatitis due to arsenical drugs was greatly facilitated in many cases by the use of sodium dehydrocholate. It is obviously difficult, if not impossible, to control such observations, in view of the fact that the hepatic damage present is subject to wide variation. This is evidenced by the fact that (a) in severe hepatitis bile salts do not provoke a choleresis and are not eliminated in the bile; (b) after the release of obstruction bile salts may not appear in the bile for from two to ten or more days; and (c) in the presence of a normal liver a choleresis produced by bile salts does not increase the

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elimination of bile pigment. Such evidence does not preclude the possibility, however, that when the liver does recover sufficiently to be stimulated by bile salts, their administration will not increase the elimination of pigment when much is present in the body. Yet, it must be remembered that much of the pigment in jaundice is in the tissue where it is relatively fixed, as compared to that in the circulation. A search of the literature has not revealed adequately controlled experiments which demonstrate that the use of bile salts increases the rate of removal of bile pigment from the blood.

An investigation of this question was begun. In our first experiments[6] anesthetized biliary fistula dogs were used and jaundice was produced by the intravenous injection of large amounts of commercially prepared bilirubin. From this study we concluded that the constant injection of 0.6 or 6.0 Gm. of sodium dehydrocholate per hour did not increase the rate of removal of intravenously injected bilirubin. However, specific mention was made, at that time, that these results would not necessarily hold true for unanesthetized dogs or human beings after the relief of common duct obstruction. Since it is difficult to obtain patients with the same degree and duration of jaundice, it was felt that this problem could best be solved by using accurately controlled unanesthetized animals. This report is concerned with the results obtained on animals "jaundiced" for the same length of time, some of which were given large doses of bile salts after the relief of common duct obstruction, while others were used as controls.

METHODS

Healthy dogs weighing between 8 and 14 kg. were used. Before operation, the animals were observed on our diet for approximately one week, and those that manifested anorexia or distemper were discarded. A total of twenty dogs was divided into two equal groups of ten dogs each; one group received bile salts, while the other group served as a control. At the first operation, under ether anesthesia, the common duct was doubly ligated and approximately 5 mm. of the duct resected between the ligatures; the gall bladder was removed. All the dogs recovered rapidly and were allowed to remain obstructed for a period of seven days. During this time they were fed the standard diet of commercial dog food and milk and were observed daily for signs of increasing jaundice, infection, anorexia, and general condition. At the end of this seven-day period, the bilirubin content of the blood and urine was determined according to the method of Gibson and Goodrich.[7] These data represent the "preoperative" bile pigment values due to occlusion of the biliary passages (Tables I, II, and III). After this period of obstructive jaundice, the animals were reoperated upon under ether anesthesia and the obstruction removed by making a biliary fistula of the Rous-McMaster type.[8] This was done by putting a catheter into the proximal portion of the cut common duct

TABLE I

RATE OF ELIMINATION OF BILE PIGMENT FROM BLOOD AND URINE AFTER RELEASE OF 7-DAY COMPLETE BILIARY OBSTRUCTION
(CONTROL GROUP)

NO. AND WEIGHT OF DOG		DAYS OF OBSTRUCTION	BLOOD BILIRUBIN		URINE BILIRUBIN		TOTAL CHOLIC ACID		DIET
NO.	KG.		PREOPERATIVELY MG./100 C.C.	NORMAL IN DAYS	PREOPERATIVELY MG./100 C.C.	NORMAL IN DAYS	MG./24 HR.	NORMAL IN DAYS	NORMAL IN DAYS
1	9.5	7	24.8	4	13.6	3	1,246	5	2
2	10.0	7	3.3	4	–	4	1,044	6	3
3	15.0	7	6.3	5	18.0	4	1,010	3	3
4	8.4	7	2.8	4	8.1	4	1,486	4	2
5	11.1	7	7.3	13	9.4	12	1,054	10	8
6	8.4	7	4.1	4	9.0	2	1,412	4	2
7	8.4	7	10.6	12	11.6	12	840	9	9
8	12.0	7	10.0	4	8.7	4	1,187	3	2
9	12.0	7	10.2	6	23.9	4	1,495	5	2
10	9.0	7	9.7	6	23.5	5	1,093	4	4
Average	10.4	7	8.9	6.2	13.9	5.4	1,187	5.3	3.4

TABLE II

EFFECT OF KETOCHOLANIC ACIDS IN PROMOTING ELIMINATION OF BILE PIGMENT FROM BLOOD AND URINE AFTER RELEASE OF 7-DAY COMPLETE BILIARY OBSTRUCTION (BILE-SALT GROUP)

NO. AND WEIGHT OF DOG		DAYS OF OBSTRUCTION	BLOOD BILIRUBIN		URINE BILIRUBIN		TOTAL CHOLIC ACID		DIET
NO.	KG.		PREOPERATIVELY MG./100 C.C.	NORMAL IN DAYS	PREOPERATIVELY MG./100 C.C.	NORMAL IN DAYS	MG./24 HR.	NORMAL IN DAYS	NORMAL IN DAYS
1	10.0	7	6.8	6	3.6	6	1,464	4	3
2	12.0	7	8.5	4	7.5	3	1,020	6	3
3	11.1	7	6.2	5	8.0	5	1,800	3	2
4	10.0	7	5.0	4	6.5	3	1,053	6	5
5	10.0	7	8.3	5	21.0	5	1,016	7	5
6	8.4	7	4.5	5	2.2	3	896	6	Ate very little
7	9.0	7	4.5	5	2.9	3	782	6	Ate very little
8	10.5	7	9.0	6	13.2	6	972	6	2
9	8.4	7	5.6	5	15.4	3	1,050	6	3
10	10.0	7	8.8	7	4.5	6	1,306	4	2
Average	9.9	7	6.72	5.3	8.48	4.3	1,136	5.4	3.0

TABLE III

COMPARISON OF AVERAGE RESULTS OBTAINED IN CONTROL AND BILE-SALT GROUPS

NO. AND WEIGHT OF DOG		DAYS OF OBSTRUCTION	REGIME	BLOOD BILIRUBIN		URINE BILIRUBIN		TOTAL CHOLIC ACID		DIET
NO.	KG.			PREOPERATIVELY MG./100 C.C.	NORMAL IN DAYS	PREOPERATIVELY MG./100 C.C.	NORMAL IN DAYS	MG./24 HR.	NORMAL IN DAYS	NORMAL IN DAYS
10	10.4	7	Control	8.9	6.0	13.9	5.0	1,187	5.0	3
			average							
			range	2.8–24.8	4–13	8.1–24	3–12		3–10	
10	9.9	7	3 Gm. ketochol/day	6.7	5.0	8.5	4.0	1,136	5.0	3
			range	4.5–9.0	4–7	2.2–21	3–6		3–7	

and bringing the rubber tubing to the outside, where the bile was collected in a rubber balloon which was attached to the outside of the dog's binder. One group of ten animals was fed 3 Gm. of ketocholanic acid (ketochol) daily with the meals; the other group was not given any bile salts. We have used this bile salt preparation since we knew from previous studies[9] that this preparation is a potent choleretic and would possibly have as much effect on the elimination of bile pigment from the blood as any of the bile salt preparations. The animals were then observed until the jaundice disappeared and the pigment content of the blood and urine became negligible. Daily blood and urine van den Bergh determinations were made to follow the pigment excretion, and the bile was analyzed for cholic acid according to the Reinhold and Wilson modification of the Gregory-Pascoe method.[10] Those animals that did not eat or those that showed signs of infection and obstruction were not included in the results. If they were included, our experiment would not be adequately controlled; i.e., we have kept conditions as uniform as possible, except for the presence or absence of bile salts and choleresis.

RESULTS

Pigment Excretion.—Control Group.—After seven days of biliary obstruction, the blood bilirubin concentration averaged 8.9 mg. per cent (range 3.0 to 24.8 mg. per cent), while the urine bilirubin concentration averaged 13.9 mg. per cent (range 8.0 to 23.9). The average time for the disappearance of the bile pigment from the blood and urine was six and five days, respectively. Most of the animals had normal urine and blood pigment concentrations in three or four days, but in two cases, Dogs 5 and 7, approximately two weeks were required for the complete removal of the excess pigment. These two dogs did not eat so well as the others, which means they were more affected by the condition than was indicated by the bilirubin data or the intensity of jaundice.

Bile-Salt Group.—When 3 Gm. of ketocholanic acid was administered daily the accumulated bile pigment was removed from the blood in five days and disappeared from the urine in four days. The preoperative blood and urine pigment concentrations were 6.7 and 8.5 mg. per cent, respectively, which was slightly less than the values obtained in the control group. Tables I and II give the results of the individual groups and Table III contains the average results as a basis for comparison. It is obvious from these results that the administration of a potent choleretic in large daily doses did not significantly increase the rate of removal of bile pigment from the blood.

Recovery of Cholic Acid Output.—What effect does the administration of bile salts have on the speed of recovery of cholic acid synthesis after the relief of common duct obstruction? In this work we had an

excellent opportunity to study and attempt to answer this practical clinical question. In both groups, cholic acid was found in the bile specimens during the first day after release of the common duct obstruction. The concentration of cholic acid became normal in one or two days, but the total daily cholic acid output did not become normal, in both the control and bile-salt group, until the fifth postoperative day on the average. None of the animals approximated normal total cholic acid output in less than three days, while only three of the twenty dogs took more than six days for cholic acid recovery. The average total daily cholic acid output in the control group was 1,187 mg., the range being from 840 to 1,495 mg. per day. In the bile-salt group the average daily output was 1,136 mg. with a range of 782 to 1,464 mg. These average figures compare favorably with the normal control values obtained in a previous study[9] on approximately seventy-five biliary fistula dogs. Thus, it is quite apparent that the administration of bile salts did not increase the speed of cholic acid recovery after relief from biliary obstruction. The results of previous studies show that cholic acid synthesis is not affected by ketochol or the ketocholanates, which is the reason why ketochol is advantageous for a study of this type. If we had used natural bile salts or nonoxidized cholic acid derivatives, we should have had to calculate cholic acid synthesis.[9]

DISCUSSION

By a series of controlled experiments we have attempted to answer the question: "Does the administration of bile salts increase the speed of disappearance of jaundice and return of cholic acid output after the relief of biliary obstruction?" It is evident from the results shown in Table III that large doses of ketocholanic acid had no significant effect on the rate of elimination of bile pigments from the blood and urine, though the average trend, which may have been due to chance, is favorable. The bile pigment was removed from the blood and urine in the control group in six and five days, respectively; five and four days, respectively, in the bile-salt series. Although there is a difference of one day between the control and bile-salt groups, this is in no way statistically significant, especially since there was much overlapping in the two groups, and since the preoperative blood and urine pigment concentrations in the treated group was less than the control group. We find that these results may have been predicted by the results obtained on total pigment output when large doses of bile salts and acids were administered to normal dogs and normal biliary fistula dogs. Dragstedt and Mills[11, 12] in a few experiments on unanesthetized dogs found that the intravenous injection of sodium dehydrocholate had no effect or appeared to augment slightly the rate of removal of intravenously injected bilirubin. In previous studies[9] we found that the daily administration of 3 and 5 Gm. of the salts of various bile acid preparations

to healthy biliary fistula dogs did not increase the daily pigment output over the control values. Thus, we have shown that the administration of bile salts will not definitely increase the rate of removal of bile pigment from the blood in normal and pathologic experimental animals.

Since the bile acids have been shown to be a product of the liver exclusively,[13] a number of investigators have determined the bile acid concentration in drainage bile and have used this test as an index of hepatic function. Greene, Walters, and Fredrickson,[14] in a group of 9 patients with gall bladder or common duct drainage, showed that in 3 patients with biliary obstruction, but possessing normal livers, the total bile acid output, determined as glycocholic acid, reached the maximum output of approximately 2.0 Gm. per day about the fifth or sixth postoperative day. In those patients with cirrhotic livers or severe hepatitis and cholangitis the cholic acid output was less than 0.5 Gm. per day after two weeks of drainage. Ravdin and co-workers[15] studied liver bile obtained by means of a T-tube from 19 patients with complete common duct obstruction of a week's duration or more. In no case were bile acids present in the first specimens obtained, and generally bile acids, as determined by the Gregory-Pascoe method, first appeared from one to four weeks after release of the obstruction depending on the degree of liver damage and cholangitis. However, no attempt was made to correlate the duration of obstruction with the return of bile acids in the bile. Gray and co-workers,[16] in a group of 50 patients with T-tube drainage of the common duct, because of occlusion, found that in 21 cases with a "normal" liver, diagnosed by inspection, the concentration of bile acids gradually reached a fixed level of 2.0 Gm. per 100 c.c. of bile on the fifteenth to the twenty-first days. In 29 patients who showed varying degrees of liver damage, classified as mild to severe, the bile acid concentration ranged from 1.1 to 0.1 Gm. per 100 c.c. respectively, on the fifteenth day. Greene and co-workers,[17] in a recent report, found in 25 patients with apparently "normal" livers, that the bile salt concentration of 800 mg. per cent was reached in five days after relief of common duct obstruction. In those cases with moderate or severe liver damage, the recovery was much slower and some of the severe cases never returned to normal during the period of drainage. Further, these investigators administered mixed bile salts to the patients in their series and found that this treatment had no effect on the concentration of bile salts in the fistula bile but did markedly improve the clinical condition of their patients, a fact which we have noted in a large number of our biliary fistula dogs suffering from partial obstruction or hepatitis.

In our series of twenty animals in which release of common duct obstruction was performed seven days after the occlusion of the duct, the total daily cholic acid output returned to normal in approximately

five days. In two dogs, Nos. 5 and 7 of the control group, the cholic acid recovery occurred only after ten and nine days, respectively. These animals refused to eat during the early postoperative period and only began to eat about one week after the operation. Two animals in the bile-salt series, Nos. 6 and 7, had low cholic acid outputs of 896 and 782 mg. per day, which can be attributed to the fact that these animals ate very little during the recovery period. Thus, anorexia and diet are important factors in the recovery of cholic acid output after relief of biliary obstruction. Greene and associates[17] have reported that the administration of large amounts of dextrose by venoclysis improved the bile salt secreting function of the liver. Further, our results and those of Greene and co-workers[17] show that the administration of bile salts was not efficacious in increasing the concentration or total daily output of bile acids in fistula bile. We used large amounts of a potent choleretic, 3 Gm. of ketocholanic acid daily, since we believed that a brisk choleresis would "flush out" the biliary passages and thus tend to aid in the recovery of the liver. It must be kept in mind, however, that a severely diseased liver can secrete copious quantities (cholerrhagia[18]) of a highly pigmented bile which contains little or no bile salts, or can secrete a pigmented bile which contains no bile salts.

SUMMARY AND CONCLUSIONS

We have studied the effect of bile salt administration on (1) the elimination of bile pigment from the blood and urine, and (2) the recovery of cholic acid after release of common duct obstruction. Jaundice was produced in twenty dogs by doubly ligating the common bile duct and resecting a portion of the duct. After seven days of complete obstruction, the animals were converted into biliary fistula dogs according to the Rous-McMaster method. One group of ten animals was fed bile salts while the other group of ten animals served as a control. Three-gram daily doses of ketocholanic acid (ketochol) during the postoperative recovery period did not increase the rate of removal of the excess bile pigment from the blood and urine. In both groups the pigment disappeared from the blood and urine in approximately five days. The normal total cholic acid output of approximately 1.2 Gm. per day occurred, in both groups, on the average, five days after release of the common duct obstruction. It was found that the early return of preoperative eating habits was an important index of the recovery of cholic acid; whereas, the administration of bile salts seemed to play a minor role in improving the bile salt secreting function of the liver. Since we have found previously that the administration of bile salts to animals with complete obstruction of the common bile duct does not affect longevity and does no apparent harm,[19] the administration of bile salts in the presence of a damaged liver is not contraindicated.

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BLOOD STUDIES DURING ANESTHESIA

Reference to Infections and Noninfections

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MANY factors are involved in the causation of convulsions during anesthesia. Primarily the condition of the patient and the nature of the anesthetic agent are directly concerned with each occurrence. There have been noted various phenomena which are coincident with these convulsive seizures; namely, overdosage of the anesthetic, encephalopathy with nitrous oxide, impurities in the anesthetic agent, acute toxemia with associated hyperpyrexia, ether diathesis, excessive carbon dioxide, anoxia, overdosage of atropine, and numerous others.[1] The majority of the reported convulsions have been associated with severe infections, although they may occur in cases with no infection and during anesthesias of short duration.

Considerable experimentation has been performed by other workers concerning the blood changes during anesthesia. The majority of these studies were conducted during ether anesthesia. A recent study by Fay and others[2] has shown that base bound by protein is decreased significantly during one hour of ether anesthesia. Several investigators[2-4] have reported a depression of serum calcium during anesthesia with ether. McAllister[5] found that administration of this agent for one hour in operative patients caused an average drop in plasma volume of 11 per cent. This loss, when calculated from the rise in plasma protein, was 9.3 per cent. Further evidence is presented by Searles,[6] showing that cell volume, platelets, and erythrocytes were increased during ether anesthesia. This was attributed to hyperventilation with increased water loss and to a contraction of the spleen, forcing more red blood cells into the general circulation. Splenectomy reduced this change by approximately one-half.

Anesthesia by intravenous injection of barbiturates has been shown to produce little alteration in the blood constituents. Bourne and coworkers[7] found a lowered pH, decreased carbon-dioxide combining power, and hydremia. Searles[6] and Higgins and Corwin[8] reported a lowering of the specific gravity of the blood during amytal anesthesia in animals. This was shown to be due to a dilatation of the spleen, with an erythrocytic influx from the circulating blood. Hydration of the blood has been noted by Bollman and associates.[9]

Peritonitis produces changes in the blood which are referable to dehydration, destruction of protein incident to infection and toxemia, and alkalemia from a chloride loss by vomiting. Orr and Haden[10] found an

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early drop in chloride concentrations occurring with experimental peritonitis in dogs. They report also a rise in urea and nonprotein nitrogen with inconstant variations in the carbon-dioxide combining power of the plasma. In those cases in which alkalosis becomes well established, there is a simultaneous rise in the combining power of the plasma for carbon dioxide.

In the light of previous investigations and prompted by the occurrence in two operative patients of typical anesthetic convulsions, the following studies were carried out. An attempt was made to determine in both the operative patient and the experimental animal the changes, incident to anesthesia, in blood concentration, plasma water, plasma protein, and the available ionic serum calcium.

MATERIALS AND METHODS

Part I. Surgical Cases.—Blood studies were performed on operative patients in the University Hospitals. Samples were obtained preoperatively, during the course of the anesthesia, and at the conclusion of the operation. The cases were those admitted with acute septic processes. Essentially, these consisted of local or general peritonitis resulting from perforated gangrenous appendicitis. Studies of the blood were also carried out during anesthesia for noninfected conditions. In this manner there was formed a control series for this group.

Part II. Experimental.—Blood examinations similar to the above were conducted on the dog: An attempt was made to parallel the state seen in the control cases in Part I. Production of peritonitis with subsequent observation of the blood during anesthesia was carried out. In these experiments the animals were anesthetized by two methods: (a) A 6.4 per cent solution of sodium pentobarbital (nembutal) was injected intravenously, in the proportion of 64 mg. of drug per 5 pounds of body weight. (b) Ether was administered by the open-drop method, with an attempt to secure complete anesthesia with a minimum of excitement in the animal.

Peritonitis was produced by the following methods:

A. *Bacterial Injections.*—Intraperitoneal injections of a virulent strain of *B. coli*, grown on twenty-four hour plain agar slants and suspended in 6 per cent gum acacia solution or 12 per cent mucin solution,[11] were given. Ten cubic centimeters of the acacia solution, containing approximately one billion organisms per cubic centimeter, was injected. Five cubic centimeters of the mucin solution was given. This contained approximately five hundred million bacteria per cubic centimeter. Each of these methods produced peritonitis of varying severity within eighteen to forty-eight hours.

B. *Aseptic Peritonitis.*—Aseptic peritonitis was produced by the method of David[12] by intraperitoneal injections of 15 per cent turpentine-water emulsion. One cubic centimeter of the emulsion was used per kilogram of body weight. This method produced fibrinous peritonitis

with transudate within forty-eight hours. Best results were obtained after two consecutive injections twenty-four hours apart.

C. *Perforation Peritonitis.*—This was produced by ligation of the appendix and its mesentery. In a few instances, the descending colon was perforated or a portion of the mesentery of the ileum ligated. All of the above operative procedures resulted within forty-eight to seventy-two hours in a progressive fatal peritonitis in approximately 60 per cent of the animals. In those surviving, there was a local peritonitis or a less active generalized nonfatal infection. Confirmation autopsies were performed.

Normal blood samples were obtained on all dogs before peritonitis was produced. A specimen was taken at the height of the infection. The dog was then anesthetized and samples were drawn at hourly intervals for two or three hours. The control animals were similarly anesthetized, a normal sample obtained as soon as deep anesthesia was reached, and at hourly intervals for two or three hours.

Examinations of the blood of the operative cases and experimental animals were in most instances conducted as follows. Each sample was divided into two 1 c.c. portions, to each of which was added 1 mg. of heparin, and a 12 c.c. portion which was allowed to clot for serum. Evaporation was prevented by sealing the tubes immediately after the blood was taken. The two smaller samples were used in the determination of the specific gravity of the whole blood and plasma. The falling drop method of Barbour and Hamilton was employed.[13] Total serum calcium was determined by the Clark-Collip modification of the Kramer-Tisdall method.[14] Plasma protein was calculated from the plasma specific gravity according to the formula of Moore and Van Slyke.[15] Ionized calcium concentrations were then read to the nearest tenth of a milligram from the nomogram adapted for clinical use by McLean and Hastings.[16] The ionic calcium fraction varies directly as the total concentration, and indirectly with protein content of the plasma, and if these two are known for any plasma sample, calculations can be made from their nomogram, calibrated by the frog heart method.

DISCUSSION

It is an established clinical fact that anhydremia, from water loss or deprivation, results in concentration of the blood with an equivalent or nearly equivalent increase of its formed elements and chemical constituents. Hydremia produces a similar proportionate decrease in blood constituents.

In the experimental animal this proportionate change was not found in peritonitis, either before or during anesthetization. With the development of peritonitis there was noted an average decrease in serum calcium of 0.4 mg. (Figs. 3 and 4). This diminution in calcium, although closely approximating the limits of variation for the chemical determination, appears to be significant in the light of the expected rise incident to

hemoconcentration, shown by an elevated specific gravity of whole blood and plasma. Ionized calcium fractions diminished with the fall in the total amount. Approximately 80 per cent of the entire group of peritonitis cases show such a decrease. The variable results in the remaining number are perhaps explained by the multiplicity of factors involved in the production of experimental peritonitis; namely, the time element (some infections developing within twenty-four to forty-eight hours, others requiring three to five days), variations in the amount of fluids consumed, degrees of infection present, and others.

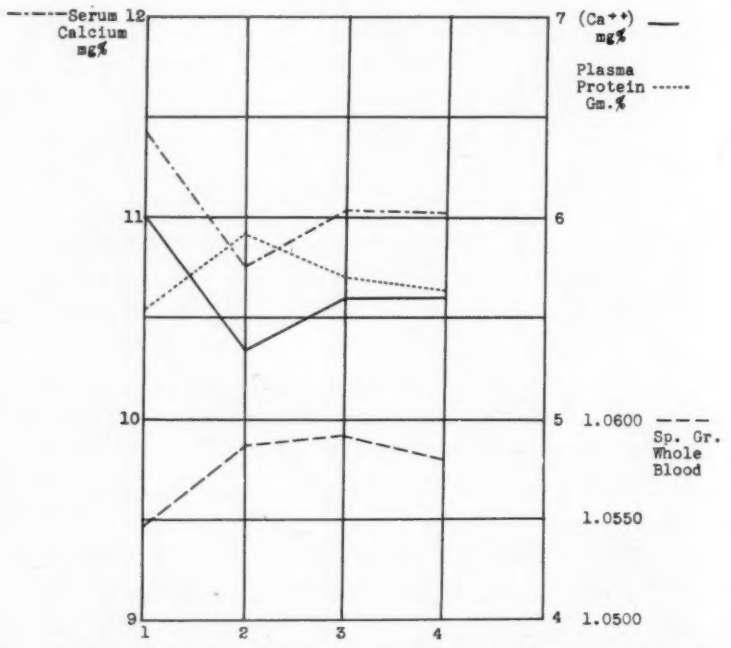

Fig. 1.—Composite graphs of controls, ether anesthesia. *1*, Pre-experimental sample; *2*, after one hour of anesthesia; *3*, after two hours of anesthesia; *4*, after three hours of anesthesia.

In the control dog, ether anesthesia produced an increased water loss. Moreover, calcium decreased, instead of increasing proportionately with the blood protein in the process of dehydration. An average fall in calcium of 0.7 mg. is observed during the first hour (Fig. 1). At the end of three hours the total amount had not reached its original level. Ionized concentrations were lowered with the total calcium. The change in the ionized portion was a result of the simultaneous decrease of the total amount and the rise in the plasma protein.

Barbital anesthesia, by intravenous injection of sodium pentobarbital in dogs of the control group, did not produce the progressive depression of ionized calcium as did ether. With the use of this anesthetic there occurred hydration of the blood, with a resultant hemodilution. This can be explained partly by an increased splenic reserve of red blood cells and partly as being due to an action inherent in the pharmacodynamics of the drug itself. This latter action is observed as an increase in plasma

water, as shown by the progressive fall of plasma protein concentrations. (Fig. 2.) The diminution in calcium was apparently proportional to the degree of hydration and is evidenced by the fixed ionic calcium concentrations during the two-hour period.

The administration of ether for a period of one hour to dogs with peritonitis caused a further depression of the total serum calcium, an average of 0.64 mg. (Fig. 3). The decreases in the ionized fractions, initiated by falling total concentrations, were aided by the rising protein content. The end of two hours of anesthesia was marked by no further variation in total calcium, and only a slight rise in ionic calcium, resulting from a decrease in protein. This latter decrease shows a return of water into the plasma, in spite of the continued increase of whole blood specific gravity.

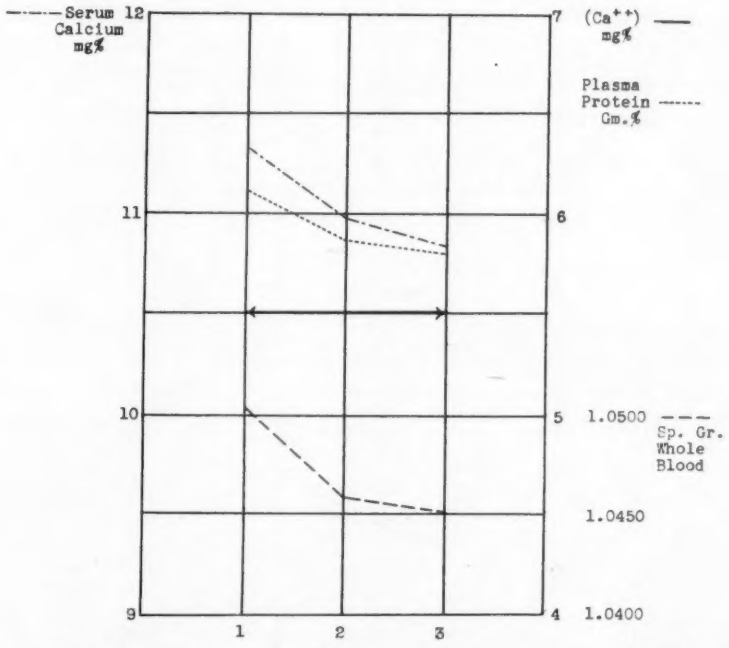

Fig. 2.—Composite graphs of controls, nembutal anesthesia. *1*, Pre-experimental sample; *2*, after one hour of anesthesia; *3*, after two hours of anesthesia.

In the peritonitis group given intravenous anesthesia, the progressive fall in total serum calcium was observed. At the end of one hour little change is noted in total calcium, and a rise in the ionic fraction is apparent. This is explainable by an increase in plasma water, reducing the protein concentration and consequently releasing more calcium in the ionized form. It has been shown that barbiturate anesthesia in dogs produces a fall in rectal temperature of two to three degrees.[7] This change, best shown during the second hour of anesthesia, resulted in hemoconcentration and an increased whole blood specific gravity. The concentration observed in this infected group appeared to be of greater magnitude than that seen in the controls and overshadowed the hemo-

dilution usually apparent with this anesthesia. By two hours, total calcium had fallen markedly, but protein concentration remained rather constant. Ionized calcium, rising at one hour, diminished by the end

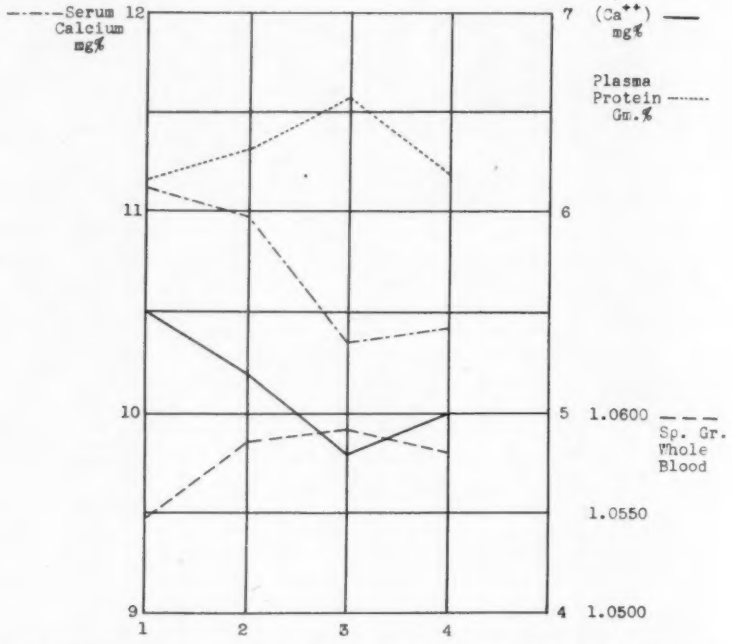

Fig. 3.—Composite graphs of peritonitis, ether anesthesia. *1*, Pre-experimental sample; *2*, height of infection, just before anesthesia was given; *3*, after one hour of anesthesia; *4*, after two hours of anesthesia.

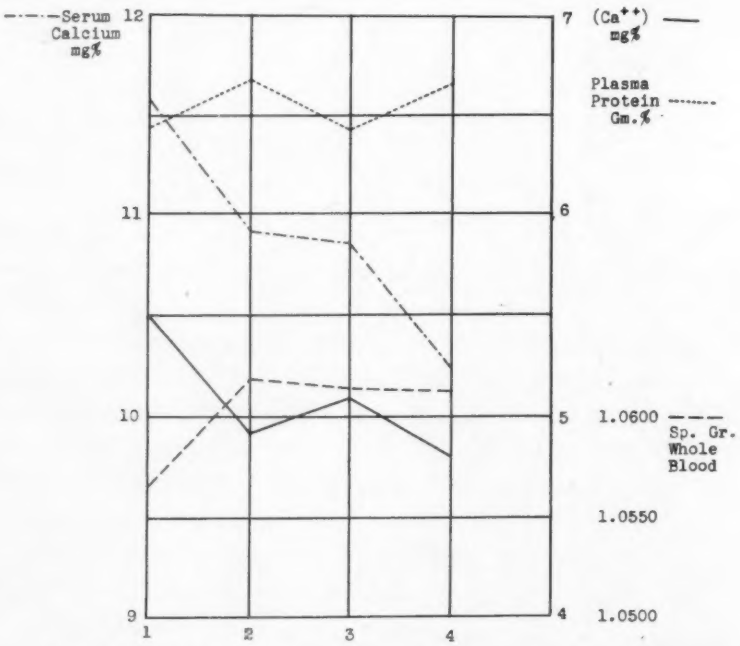

Fig. 4.—Composite graphs of peritonitis, nembutal anesthesia. *1*, Pre-experimental sample; *2*, height of infection, just before anesthesia was given; *3*, after one hour of anesthesia; *4*, after two hours of anesthesia.

of the second hour, concurrently with the fall in the total amount. It will be noted that these results do not parallel those in the group of controls (Fig. 2).

The above findings in the experimental animal group were essentially substantiated in the blood studies on the operative patient. A total of 27 patients were observed, of whom 16 had ether anesthesia and 11 cyclopropane. Each of these groups was further subdivided into the noninfected cases, comprising the controls, and those with septic processes.

The control cases, given cyclopropane anesthesia, exhibited an average drop of 1 mg. in total serum calcium during the operative procedure, with a gain of 0.6 mg. at the conclusion of the operation. The cases with infection, however, showed a progressive drop in total serum calcium, an average of 0.4 mg. during the procedure, with an additional decrease of 0.3 mg. by the end of the anesthesia. In all cases, the degree of the depression of the calcium seemed to depend upon the length of the anesthesia. The average length in this series was forty-five minutes.

In the group with ether anesthesia similar changes were noted. The control cases exhibited an average decrease in total serum calcium of 0.75 mg. and in ionic calcium of 0.1 mg. during the time required for operative procedures. Those patients with sepsis were shown to have an average fall of 0.8 mg. in total calcium and of 0.3 mg. in the ionized fraction, during the time for operative procedures. The rather marked changes that occurred in some of these patients are exemplified by the findings in Case 2. Here the preoperative total calcium level was 11.90 mg., the midoperative sample 10.20 mg., and at the conclusion of the anesthesia, 9.94 mg. per cent, a total drop of nearly 2 mg. This patient had acute gangrenous appendicitis, with local peritonitis. In Patient H. P., acute cholecystitis requiring cholecystectomy, an ether anesthesia of one hour and fifteen minutes' duration caused a fall in calcium (total) from 11.80 mg. to 10.05 mg. per cent, a decrease of 1.75 mg.

In view of the fact that the above averages in hospital cases do not present the striking results seen in the experimental animal, it should be pointed out that with these patients the anesthesias were of shorter duration and the processes less acute. The calcium depression, noted clinically, is substantiated by the more carefully controlled experimental work with animals.

SUMMARY

There is probably no individual factor or single group of factors responsible for the production of convulsive seizures during anesthesia. It is realized that conditions vary widely with each patient, and that in any convulsion one or more groups of diverse factors or any combination of these may be responsible.

Observations during convulsions in operative patients have been made by other investigators. In the majority of cases the convulsions oc-

curred in the presence of severe sepsis and near the termination of the anesthesia. In many instances, the control of the seizure was effected by administration of a calcium salt intravenously.

This study consists of examination made upon the blood of operative patients and experimental animals during anesthesia, both in the normal state and in the presence of sepsis. Studies of the amount of available calcium and degree of dehydration and hydration of the blood were carried out.

It has been found that the available ionic calcium in the blood is decreased during ether anesthesia. The duration of the anesthesia apparently determines the degree of lowering of the calcium level.

Acute abdominal infections effect a decrease in ionized calcium in both the operative patient and experimental animal. This change is further augmented during anesthetization with ether.

The use of intravenous sodium pentobarbital does not significantly affect the ionic calcium levels in the control or septic state.

In no instance, either experimentally or clinically, was there noted a lowering of the calcium levels to within the limits of those seen in tetany.

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DYNAMIC CHANGES IN EXPERIMENTAL PULMONARY EMBOLISM*

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INTRODUCTION

AN EXTENSIVE literature has accumulated dealing with the hemodynamic changes and the mechanism of death following clinical and experimental pulmonary embolism. This has been adequately reviewed in the past (Mendlowitz,[1] de Takats,[2] Horn[3]). These studies suggest that pulmonary embolism is followed by an elevation in pulmonary arterial pressure. Clinically, however, such evidence is inferential, no method being as yet available to record the pulmonary pressure in man. Experimentally, direct determinations of the pulmonary arterial pressure have not been made in normal anesthetized or unanesthetized animals. The latter would permit a correlation with other circulatory changes and would make possible a better evaluation of the ensuing circulatory adjustments. In addition such studies would help in determining the evolution of the various changes leading to death and would thus help in establishing the therapeusis on fundamental physiologic principles. Such a method is now available[4-6] and the perfection of technique in its use in our laboratory[7] has led us to reinvestigate the dynamic changes following experimentally produced pulmonary embolism.

METHODS

The technique of applying the cannula about the pulmonary artery[7] consists essentially in the application, under strictest asepsis, of a specially designed silver cannula around the pulmonary artery by an exposure through the third or fourth left intercostal space. The incision is closed tightly in layers, all the air entrapped in the pleural cavity removed and the dog is then allowed to recover.

In an attempt to simulate as closely as possible the syndrome of clinical pulmonary embolism, observations have been carried out in three types of preparations, namely: (1) With an embolus composed of Penrose tubing filled with fluid, similar in all respects to that described by Mendlowitz.[1] This is analogous to clinical involvement of the main pulmonary artery or its two major divisions. (2) With emboli composed of pea seeds, prepared and administered according to the method of Binger, Brow, and Branch.[8] This is the counterpart of multiple

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clinical embolism of the moderately sized radicles of the pulmonary arteries. (3) With emboli composed of starch granules suspended in saline solution prepared and administered, except for a more rapid injection rate and larger dosage, according to the method of Binger and co-workers.[9] This simulates multiple clinical embolism of the pulmonary arterioles and capillaries.

Fourteen dogs were used in this study. One week following insertion of the pulmonary cannula, the animal was prepared for the type of embolus desired. Both before and at frequent intervals following induction of pulmonary embolism, simultaneous pulmonary and systemic arterial blood pressures were obtained using the Hamilton needle manometer,[10] according to the technique previously described by us.[11] Arterial pulse wave contours were obtained at fast camera speeds to demonstrate that the needles were within the arterial lumina. Systemic venous pressure was recorded by a water manometer from one of the superficial veins of the forelimb. The respiratory rate was determined by actual count over one minute, while the heart rate was determined from the optically recorded pressure curve.

It was possible to follow the changes after the passage of the "Mendlowitz embolus" in the unanesthetized dog, the right external jugular vein needed for the insertion of the embolus being exposed under local (procaine hydrochloride) anesthesia. On the other hand, in the experiments with pea seeds and starch granules, anesthesia was required because of the restlessness and excitement induced by the embolism in the dogs. The animals, therefore, were kept lightly anesthetized with nembutal intravenously. Subsequent studies of ours have shown that the dynamics following embolism are little if at all altered by general anesthesia.

Autopsies were performed to note the position of the emboli as well as the effect upon the heart, lungs, and other viscera, and in the starch granule experiments the extent and degree of occlusion of the pulmonary arterioles and capillaries were estimated microscopically.

RESULTS

A characteristic experiment for each type of embolism is summarized in Tables I, II, and III.

I. *Controls.*—Since the "Mendlowitz embolus" is forced into the circulation by the injection of 100 to 150 c.c. of normal saline solution, and as much as 200 c.c. of saline solution is employed in the starch emboli experiments, the changes evoked by rapid fluid administration were accordingly studied for purposes of control in two unanesthetized dogs by injecting 150 c.c. of normal saline solution in fifteen seconds through a No. 13 needle inserted into the right external jugular vein. The injection was followed by a transient rise in systolic pulmonary and systemic pressures lasting ten to fifteen minutes, respiration and heart rate

TABLE I

MENDLOWITZ EMBOLUS*

	CONTROL		IMMEDIATELY AFTER FLUID INJECTED	AFTER 15 MIN.		10 MIN. AFTER EMBOLUS WAS PASSED	20 MIN. AFTER	25 MIN. AFTER	30 MIN AFTER	1 HR. AFTER	1 HR. 15 MIN. AFTER	3 HR. AFTER	5 HR. AFTER	
Pulmonary arterial pressure, mm.Hg	30/5	150 c.c. saline solution intravenously	40/5	30/5	Embolus passed down vein	65/10	48/10	60/10	70/10	55/10	50/10	52/15	55/15	Dog died; extreme dyspnea with gasping respiration
Systemic arterial pressure, mm.Hg	120/70		140/75	130/75		150/85	160/100	120/70	150/100	120/70	130/80	120/65	125/75	
Systemic venous pressure, cm.H_2O	5						7					10	15	
Heart rate/min.	156		156	156		168	168	168	168	192	192	204	192	
Respiratory rate/min.	22		26				42		40		48	42	46	

*Necropsy, riding embolus of pulmonary artery.

TABLE II

PEA SEED EMBOLI

	CONTROL		5 MIN.*		7 MIN.*	11 MIN.*		17 MIN.*		19 MIN.*	27 MIN.*		30 MIN.*		34 MIN.*		38 MIN.*	41 MIN.*		48 MIN.*		50 MIN.*
Pulmonary arterial pressure, mm.Hg	23/ 6	9 peas injected intravenously	31/6	3 peas injected intravenously	33/8	44/13	5 peas injected intravenously	57/15	3 peas injected intravenously	65/18		5 peas injected intravenously	70/20	5 peas injected intravenously	75/25	10 peas injected intravenously	80/25		5 peas injected intravenously	50/25	5 peas injected intravenously	25/2
Systemic arterial pressure, mm.Hg	125/70		125/70		120/60	175/85		125/75		155/80			130/60		175/85		170/75			115/50		85/40
Systemic venous pressure, cm.H_2O	6				5						7							9				
Heart rate/ min.	144		180		168	168		156		156			156		168		144			144		12
Respiratory rate/min.	43		80			72		86		100	88		102		100		120			46		8

*After injection of first pea seeds.

TABLE III

STARCH GRANULE EMBOLI

	CONTROL		15 MIN.*		30 MIN.*		40 MIN.*	1 HR. 5 MIN.*		1 HR. 15 MIN.*		1 HR. 20 MIN.*		1 HR. 35 MIN.*	1 HR. 45 MIN.*	1 HR. 55 MIN.*
Pulmonary arterial pressure, mm.Hg	32/15	20 c.c. starch solution injected intravenously	40/20	20 c.c. starch solution injected intravenously	42/22	60 c.c. starch solution injected intravenously	47/30	50/30	10 c.c. starch solution injected intravenously	65/37	40 c.c. starch solution injected intravenously	90/50	50 c.c. starch solution injected intravenously	90/50	90/20	
Systemic arterial pressure, mm.Hg	150/85		140/75		135/70			150/80		160/95		160/75		175/100	140/80	Dog died
Systemic venous pressure, cm.H_2O	7						15					24			11	
Heart rate/min.	96		96		120		144	144		132		168		168	192	V.F.†
Respiratory rate/min.	20		28		28		36	52		64		80		104	120	Extreme tachypnea

*After injection of first starch solution.
†Ventricular fibrillation.

remaining unchanged. (Table I.) The slight rise in systolic arterial pressure apparently is due to the increased output of the ventricle.

In two dogs in which the Mendlowitz embolus was used, autopsy revealed obstruction of the inferior and superior vena cava respectively, These dogs may therefore serve as further controls. In one of these animals the embolus was found lying in the cavity of the right auricle partially obstructing the inferior vena cava. No changes were noted in this animal over the three-hour period of observation. At the end of this time the dog was sacrificed and at autopsy the heart appeared grossly normal. In the other animal in which the embolus at autopsy was found lying partly within the superior vena cava and partly within the right auricle, no change in pulmonary pressure, systolic arterial pressure, or heart rate was observed. However, a slight increase in the rate and amplitude of respiration and a tremendous increase in the venous pressure were noted. The respiration gradually returned to normal, but the venous pressure remained elevated during the entire period measured. At autopsy, the heart and lungs appeared grossly normal. The obstruction was sufficient in this animal to have induced a superior vena cava syndrome.

II. *Effect of Major Pulmonary Embolism.*—Major pulmonary embolism using the Mendlowitz embolus was successfully induced in 4 dogs. In 2 of these dogs a riding embolus of the main pulmonary artery was found at necropsy and in the other 2 dogs a complete embolic occlusion of the right branch of the pulmonary artery had occurred. In all 4 animals the right heart appeared markedly dilated, while the coronary veins stood out distinctly and definitely overshadowed the coronary arteries. In 1 dog which died seven minutes after passage of the embolus, the lungs appeared pale and ischemic; in the remaining 3 dogs, in which death did not occur for periods of four to forty-eight hours, the lungs presented gross evidences of early pulmonary edema with focal areas of congestion. All 4 animals presented moderate to marked passive hyperemia of the liver. No other significant abnormalities were evident at necropsy.

The passage of the embolus was followed by an abrupt increase in both systolic and diastolic pulmonary pressures. The rise persisted with minor fluctuations throughout the period of observation. In 2 dogs a relatively small rise in systemic systolic and diastolic pressures occurred; in the other 2 no change was observed. After a variable period, the systemic arterial pressure tended to fall, reaching shock level in one dog. Venous pressure rose in the 3 animals in which it was measured. In 1 dog in which multiple readings were obtained, it was found that the elevation in venous pressure was gradual over a period of hours and occurred some time after the rise in pulmonary pressure. This would indicate the time lag necessary to induce a degree of venous distention great enough to record venous pressure elevation.

Dyspnea and moderate tachypnea were noted usually coincidentally with the rise in pulmonary arterial pressure. The changes in respiration tended to become progressively more severe, until terminally when respiration usually slowed markedly and became gasping in character. Cyanosis appeared at some variable time after embolism and when once apparent it progressively intensified.

Tachycardia followed embolism in 2 dogs; presumably terminal ventricular fibrillation superseded the sinus mechanism in 1 of these animals. In the other 2 animals the changes in rate were minimal, except that terminally the rate slowed in 1 of them.

III. Effect of Minor Multiple Pulmonary Embolism.—

A. Multiple Embolism of Moderately Sized Arteries.—At autopsy, in the 4 dogs in which pea-seed embolism was studied, the findings were similar to those described by Binger and associates.[8] The seeds were covered with fibrin and ante-mortem clot and appeared to have completely occluded the moderately sized branches of the pulmonary artery. The lungs were characteristically pale containing minimal quantities of blood while the right heart was constantly dilated.

The mode of seed administration varied in the different animals. Two dogs received a total dose of twenty peas at one time, while the other 2 dogs received thirty-five and fifty pea seeds in divided doses, respectively. The characteristic response to seed embolism was an abrupt rise in systolic and diastolic pulmonary pressures. Whether administered in single or divided doses, pulmonary hypertension, once it appeared, became progressively more marked until terminally when, in the 3 animals in which readings were obtainable, the pulmonary pressure tended to fall rapidly toward zero. This would indicate that once a sufficient number of seeds have been administered to impose some resistance to blood flow through the pulmonary circuit, further elevations in pulmonary pressure become roughly quantitatively dependent upon increasing degrees of mechanical obstruction to the circulation through the pulmonary arteries. The progressive pulmonary hypertension noted following cessation of seed administration can therefore only be explained on the basis of increasing obstruction occasioned presumably by the addition of ante-mortem thrombi upon the pea seeds, or much less likely by a reflex pulmonary vasoconstriction.

The systemic arterial pressure, after fifteen to thirty minutes, rose moderately in 3 dogs. It then tended to fall to the control level and was so maintained until terminally when simultaneously with the pulmonary pressure it also declined rapidly. The venous pressure alterations in the pea-seed embolism were not striking; 2 dogs exhibited a slight rise, while the remaining dogs showed insignificant variations.

Changes in respiration occurred coincidentally with or soon after the appearance of pulmonary hypertension and consisted of progressive

dyspnea and tachypnea with an apparent increase in amplitude. Terminally, however, when the pulmonary and systemic arterial pressures began to fall rapidly, respiration slowed markedly and became stertorous. Increasingly severe cyanosis which became intense terminally was observed in all animals.

Changes in heart rate were inconstant. In 2 dogs progressive tachycardia developed, with the apparent advent of ventricular fibrillation terminally in 1 dog. In the remaining dogs variations in the cardiac rate were minimal until terminally when a marked bradycardia appeared with rates of 54 and 12 per minute. The exact nature of this bradycardia whether of sinus origin, or due to the development of complete or to partial A-V block, or to some other mechanism, was undetermined.

B. Multiple Embolism of Pulmonary Arterioles and Capillaries.—A 1:20 suspension of starch granules in distilled water was used in all 4 animals studied. Two dogs received a total dose of 50 c.c. of the suspension in one injection while the remaining 2 dogs received total amounts of 75 and 200 c.c. of the suspension, in divided doses.

At necropsy, the findings were essentially alike. The right heart appeared markedly dilated. The lungs were pale pink with no apparent gross edema fluid. Microscopically, however, small focal areas of congestion scattered throughout both lung fields were occasionally observed. In random sections, the granules appeared primarily to have occluded the arterioles, only an occasional granule being found bulging a capillary wall. Embolization was diffuse and extreme, practically all the pulmonary arterioles appearing to have been involved.

The pulmonary arterial pressure showed an abrupt rise in its systolic and diastolic levels. The elevation in pressure could be integrated with the increased pulmonary arteriolar resistance due to the mechanical obstruction by the starch granules in the arterioles, since repeated doses of the suspension produced further increments of pressure elevation. However, it was noted that one dog receiving a single dose of the suspension developed a further rise in pulmonary pressure after the initial elevation, possibly as a result of a gradual dispersion of the granules to previously nonoccluded arterioles or by reflex pulmonary arteriolar vasoconstriction. Terminally in 3 of the 4 dogs, the pulmonary pressure showed a moderate decline.

The systemic arterial pressure changes were not striking. This confirms similar observations by others.[12-14] However, an increase in pulse pressure and a fall in diastolic pressure such as has been reported by Binger and associates[9] was not observed. Noteworthy was the fact that in 1 dog each injection of starch suspension resulted in a slight fall in systemic pressure followed by a rapid return to the control level. Terminally in 1 dog the systemic pressure fell to shock levels. This fall coincided with a similar though less marked decline in pulmonary arterial pressure.

In contradistinction to Dunn[12] who observed no conspicuous venous pressure alteration we found that the venous pressure rose gradually in 3 dogs and fell in 1. This latter decline coincided with a fall in both the systemic and pulmonary arterial pressures. The data in this latter animal are significant since the pulmonary pressure was still found at mildly hypertensive levels when compared with the control readings at a time when a marked systemic arterial hypotension and a marked fall in venous pressure were present.

Coincident with the development of pulmonary hypertension, the rate of respiration increased. Once present, tachypnea progressively increased, being most marked at the time of death. In contradistinction to the labored, deepened, and more rapid respiration following major and seed embolism, the respiration following starch embolism was not labored and as the rate increased the amplitude appeared to decrease proportionally. During the period of tachypnea, cyanosis constantly developed and in all instances became intensified terminally.

In the 2 dogs in which the heart rate was determinable, progressive tachycardia accompanied the development of pulmonary hypertension and tachypnea.

DISCUSSION

A. *Circulatory Changes Following Pulmonary Embolism.*—These investigations indicate that the initial and primary effect of major and multiple minor pulmonary embolisms is an abrupt rise in systolic and diastolic pulmonary pressures. On the basis of the pea seed and starch granule embolism it would seem that up to a certain limit indicating complete obstruction the magnitude of pulmonary pressure elevation varies directly with the degree and extent of the mechanical obstruction to blood flow through the lesser circuit. It has been shown that following massive pulmonary embolism there is a fall in the minute volume output of the heart.[1] Although no measurements of cardiac output were performed in these experiments, using the systemic arterial blood pressure as one index of cardiac minute output, our results with starch embolism would offer suggestive evidence that similar hemodynamic changes follow multiple minor embolism. Such decreases in cardiac minute output appear to depend upon the degree of mechanical obstruction in the pulmonary bed. However, the relative stability of the systemic arterial pressure despite the presumptive decrease in cardiac output would indicate that the buffer nerve mechanisms caused peripheral vasoconstriction to maintain the blood pressure level.

The changes in venous pressure were variable. Sometimes it remained unchanged, more frequently it rose, occasionally it fell. Aside from the remote possibility of active local neurogenic venous vasoconstriction or dilatation, the systemic venous bed functions in a passive manner, venous pressure changes being dependent upon the relationship of cardiac out-

put to the venous return and subject to changes in the amount of blood in circulation. The effect of obstruction secondary to pulmonary embolism upon venous pressure is twofold and antagonistic. By obstructing the flow of blood through the pulmonary bed it tends to cause accumulation of blood in the right heart and systemic veins and so tends to raise the venous pressure, while by decreasing the minute volume output of the heart it reduces the venous return and so tends to lower the venous pressure. The net effect of these two actions will then determine the level of the venous pressure at any instant (except so far as changes in the amount of blood in circulation come into play). Thus when the fall in cardiac minute output is disproportionally greater than the stasis behind the pulmonary obstruction as indicated by the elevation of pulmonary pressure, the venous pressure will decrease. If on the other hand the reverse be true, the venous pressure will rise. The rise in venous pressure is to be considered as an indication of the mechanism by which the right heart is enabled to attempt to meet the heightened resistance to emptying. By increasing its diastolic volume the right ventricle is enabled to perform a greater amount of work per stroke.

Because of a decrease in cardiac output it has been postulated[1] that the essential cause of death in pulmonary embolism is a specific type of hypokinetic circulatory failure secondary to obstruction in the lesser circuit. In the majority of the experiments we noted that the venous pressure rose following pulmonary embolism. Such elevation associated with a normal systemic arterial and an elevated pulmonary arterial pressure persisted in some animals until death. In other animals, however, in spite of an elevated pulmonary pressure both the systemic arterial and venous pressures tended to fall, reaching shock levels in some instances. Such evidence would superficially indicate that some dogs died apparently as a result of a gradual failure of the right heart indicated by a rising venous pressure while others died as a result of peripheral circulatory collapse indicated by a falling systemic arterial and venous pressure. Careful analysis of the data shows that the two conditions are interrelated and are really variants of the same phenomenon. Essentially one primary mechanism is operating in the death of all these animals. We believe that the primary fault lies in the presence of a foreign object, the embolus in the pulmonary arterial tree. This object acts as a direct mechanical deterrent to the blood flow through the pulmonary circuit. If such an obstruction is not complete, the essential mechanism insuring an adequate flow is accomplished by an increase in the work of the right ventricle. With more complete obstruction the work of the right heart approaches a maximum, and when in spite of this the cardiac output begins to fall, peripheral vasoconstriction follows to aid in maintaining the blood pressure. Further obstruction leads to the

final picture presented in these experiments. Relative coronary insufficiency with consequent myocardial ischemia develops and the heart then begins to fail. Heart failure is progressive, but may be gradual,

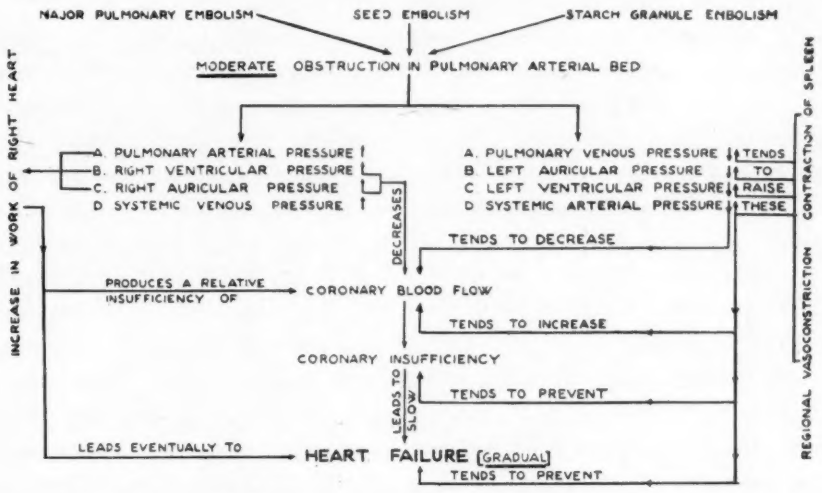

Fig. 1.—Cardiodynamics of pulmonary embolism with gradual failure of the right heart.

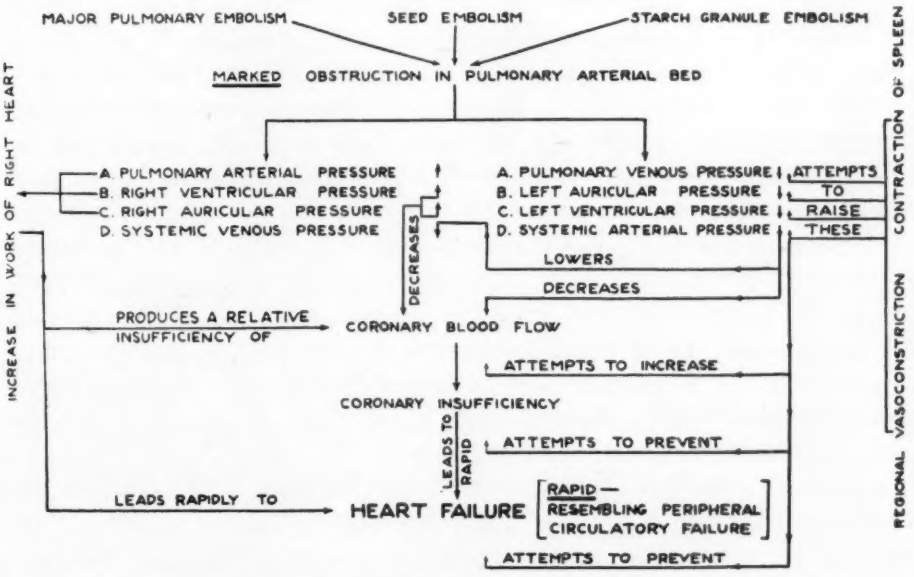

Fig. 2.—Cardiodynamics of pulmonary embolism with rapid failure of the right heart.

in which case death apparently results from extreme right heart failure (Fig. 1); or it may be rapid, in which case death presents itself as the picture of what has been termed hypokinetic circulatory failure (Fig. 2). The mechanism is, however, still the same and represents the syndrome of a right heart that cannot meet its load. This viewpoint coincides with experimental observations on the mechanism of heart failure made in this laboratory.[15]

B. *Mechanism of Death in Experimental Pulmonary Embolism.*—In these and in a series of experiments that will form the basis of subsequent reports dealing with the effects of various therapeutic agents on and the mechanism of dyspnea and tachypnea in experimental pulmonary embolism, we have observed no instance of so-called "sudden death." Pilcher[16] has stated that one need not invoke reflex mechanisms to explain sudden fatalities in pulmonary embolism, sufficient anatomic changes being always present to account for the death in such cases. Various investigators,[17, 18, 19] however, have postulated sudden vagal stimulation with reflex coronary vasoconstriction to explain cases such as these and present electrocardiographic evidence to support these contentions. As further proof they indicate that the electrocardiographic patterns are improved by abolishing vagal activity either surgically or pharmacologically. Before this view is accepted, it is necessary to consider the factors which influence coronary flow relative to the needs of the heart. As the work from this laboratory[20-24] has shown, total coronary flow depends upon a number of factors among which are: (1) the pressure in the aorta which determines the coronary driving force, the flow varying directly with the pressure; (2) the extent of extravascular compression, the flow varying inversely with the degree of compression which is determined by the distention of the heart; (3) the presence of local tissue metabolites in the myocardium which accumulate in anoxemia and ischemia and tend to dilate the coronary arteries and so increase the coronary flow; and (4) the degree of Thebesian vein and coronary sinus flow which varies inversely with the height of the pressure in the right ventricle and auricle, respectively.

Following pulmonary embolism we have demonstrated an increase in pulmonary pressure and presumably therefore in right ventricular pressure. This by increasing extravascular compression and by affecting the Thebesian veins will tend to diminish coronary flow. The elevation in right auricular pressure as shown by elevation in venous pressure also operates to decrease coronary flow by slowing the emptying of the coronary sinus and veins draining into it. When to this is added the fact that the work of the right ventricle increases as a result of the embolus, as shown by the rise in pulmonary pressure, one need postulate no theoretical coronary vasoconstriction to account for the electrocardiographic changes, for such changes can be readily explained on the basis of relative coronary insufficiency brought on by the net effect of the aforementioned factors. No change in driving force occurs to compensate for these factors since no striking change in systemic arterial pressure occurs to increase coronary flow. In fact, terminally the drop in systemic arterial pressure would be a further factor in slowing the coronary flow at that time. There is no reason to believe that metabolites of a dilator nature compensate for this decrease in relative coronary flow. In view of these facts, there is little to support the reflex theories of

death in pulmonary embolism, particularly since the nerves exert no powerful effects, and, in the dog at least, the vagal fibers are dilators.[25] It was observed that ventricular fibrillation apparently developed in some of the animals and appeared to be the immediate cause of death. It appears more logical, therefore, to believe that such an ectopic rhythm may develop in clinical cases and is the more likely cause for some cases of rapid, "sudden" or unexpected death. This ectopic rhythm, or the premature systoles that lead to it, may be of neurogenic reflex origin, with the efferent path sometimes being over the vagi. In this way rather than by a coronary vasoconstriction can the possibility of "reflex death" be accounted for.

SUMMARY AND CONCLUSIONS

1. The mechanism of death and the circulatory changes following major and multiple minor experimentally produced pulmonary embolisms have been investigated in fourteen normal anesthetized or unanesthetized dogs by directly measuring pulmonary and systemic arterial pressures, the systemic venous pressure, heart and respiratory rates. A modification of the London cannula was used to obtain the pulmonary pressure.

2. Major and multiple minor pulmonary embolisms are followed by the development of systolic and diastolic pulmonary hypertension. Systemic arterial pressure changes are not striking. Systemic venous pressure most frequently rises; rarely it falls or shows no change. Heart rate changes are inconstant. Ventricular fibrillation appears terminally in an occasional animal. Rapid respiration develops, usually coincidentally with or soon after the appearance of pulmonary hypertension, and tends to progressively increase. Most frequently progressive cyanosis accompanies the respiratory changes.

3. The theory of reflex coronary vasoconstriction as a cause of "sudden death" finds little support in these experiments, since mechanical factors are enough to explain the possible changes in coronary circulation.

4. The cause of death in pulmonary embolism appears to be due to a rapid or slow failure of the right heart, resulting from the pulmonary vessel obstruction, so-called hypokinetic circulatory failure being in reality *rapid* right heart failure.

We are indebted to Miss L. Friedberg, Mr. M. Feinstein, and Mr. R. Asher for technical assistance in these experiments.

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REDUCTION OF SUPRACONDYLAR FRACTURE IN CHILDREN

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SUPRACONDYLAR fracture of the elbow with displacement of bone fragments and marked generalized swelling about the elbow presents a very difficult problem for the physician and a serious one to the child. Immediate manipulative reduction in acute flexion is the ideal treatment of the fresh fracture before swelling develops. Manipulative reduction in acute flexion, however, is not the ideal method of treatment of the fresh fracture associated with marked swelling and blebs. I have treated this group of children during the past ten years by a method which has proved so efficient that I now wish to present it to the profession.

A Kirschner wire is drilled transversely through the proximal end of the shaft of the ulna (not through the olecranon process) to obtain four or six pounds of skeletal traction (Figs. 3 and 4). Either local or general anesthesia may be used. The line of skeletal traction is directed upward and forward in relation to the elbow since the distal fragment of the fractured humerus is posterior and proximal (Fig. 1). Counter-traction is obtained through the patient's body weight and by attaching a weight of about one to three pounds to a padded linen towel which is placed over the abducted arm (Figs. 3 and 4). The entire arm extends beyond the edge of the bed. The bed may be elevated several inches on the side of the injured arm or sand bags may be placed between the mattress and springs above and below the arm to protect the child from the danger of falling out of bed.

Ulnar or radial displacement of the distal fragment of the humerus can be corrected by digital pressure and counter pressure (Fig. 2). The hand is supported with the help of a hand grip while the forearm is supported by a circular piece of felt which is pinned to the traction apparatus (Figs. 3 and 4).

Reduction of the fracture is a gradual process. Good reduction can always be accomplished if treatment is started while the fracture is fresh or before the formation of callus. I have seen considerable callus formation in supracondylar fractures of children ten days after the injury. Anterior and lateral portable radiograms are obtained and studied as frequently as necessary.

Active exercises of the fingers, thumb, and wrist as well as pronation and supination of the forearm are encouraged at the very beginning. Active elbow exercises are started as soon as radiograms reveal callus formation. The skeletal traction treatment is continued until radiograms

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Fig. 1.—Lateral radiogram of supracondylar fracture with the usual posterior and proximal displacement of the distal fragment, elbow, and forearm. The arrows indicate the line of skeletal traction and towel countertraction on the ulna and arm respectively. The fracture is gradually reduced by the traction forces. Immediate manipulative reduction in acute flexion is contraindicated because of marked hemorrhage and soft tissue swelling about the elbow. Reduction by open operation is not necessary.

Fig. 2.—Anteroposterior radiogram of supracondylar fracture of elbow showing ulnar displacement of the distal fragment of the humerus. This displacement is readily corrected by digital pressure. The reduction is maintained by continuous horizontal traction attached to the ulnar end of the Kirschner wire. With radial displacement of the distal fragment the traction would be attached to the radial end of the Kirschner wire.

demonstrate adequate union, which is usually at the end of three or four weeks from the date of the original injury. All apparatus is then removed and the patient becomes ambulatory with the forearm and elbow supported by an ordinary sling which is removed several times daily for physiotherapy which includes active assisted objective exercises.

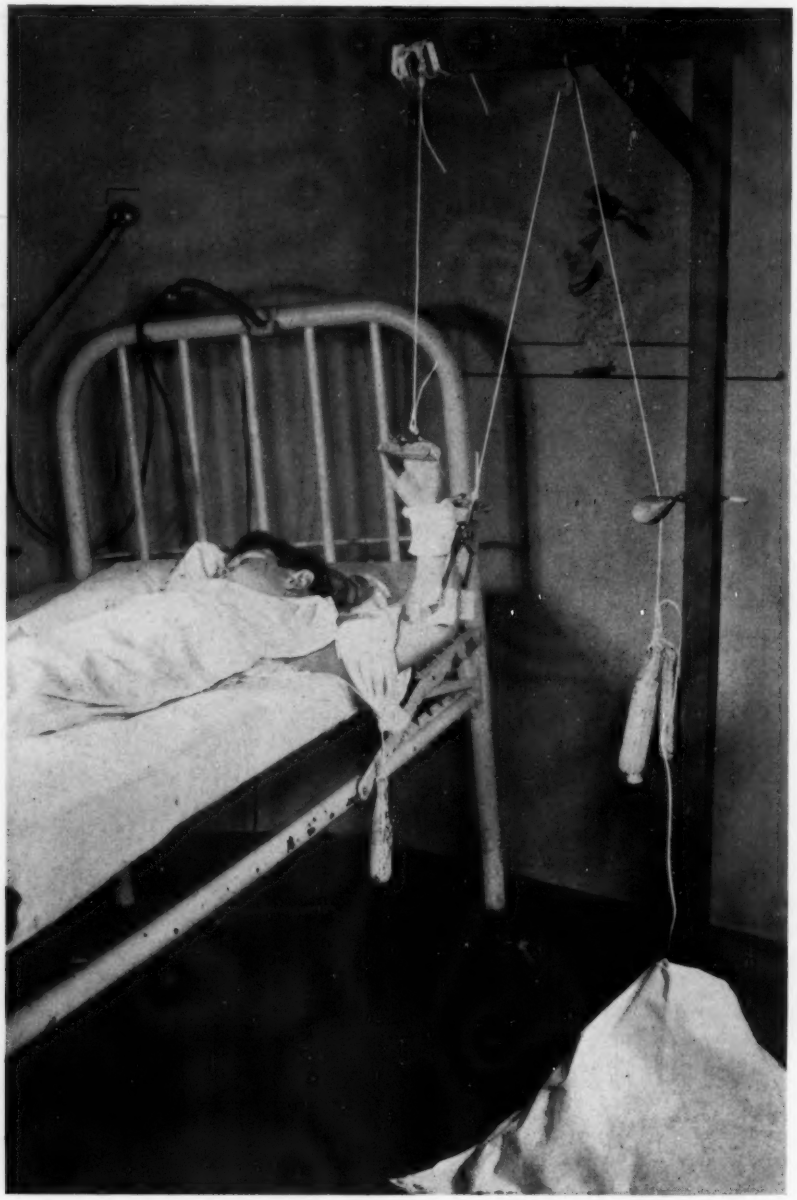

Fig. 3.

Figs. 3 and 4.—Photographs which demonstrate the gradual reduction of supracondylar fracture of children by means of skeletal traction through the proximal end of the shaft of the ulna. Note (1) the line of pull of skeletal traction, (2) padded linen towel with weight attached over the arm for countertraction, (3) hand grip, (4) forearm felt support, (5) elevation of the side of the bed, (6) aseptic treatment of the Kirschner wire, (7) swelling and blebs in the flexure of elbow, (8) exposure of the entire extremity for vigilant inspection of circulatory and neuromuscular systems.

This method of gradual reduction of supracondylar fracture in children is advised when immediate manipulative reduction fails or when manipulative reduction is contraindicated because of extensive hemor-

Fig. 4.—See opposite page for legend.

rhage and marked generalized swelling of the elbow. The method is ideal because it is mechanically efficient, the patient is comfortable, the extremity is elevated, and the entire extremity is exposed for vigilant inspection of the integrity of the circulatory and neuromuscular systems.

THE INFLUENCE OF HYPOPROTEINEMIA ON THE FORMATION OF CALLUS IN EXPERIMENTAL FRACTURE

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HYPOPROTEINEMIA has been shown to retard healing in soft tissue wounds in dogs,[1, 2] and it has recently been shown that hypoproteinemia is frequently present in patients with wound disruption.[3] These observations and the well-known relationship between the serum calcium and the serum proteins suggested that hypoproteinemia might also exert an adverse influence on the healing of fractures. In 1937 Kernwein[4]

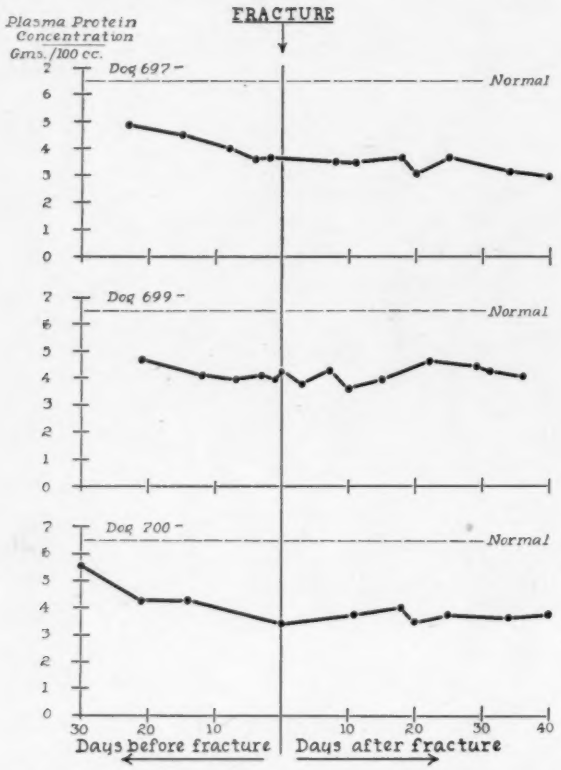

Fig. 1.—Plasma protein levels of hypoproteinemic dogs from before time of fracture until hypoproteinemic regimen was completed.

found that fracture healing in rabbits was retarded by starvation. A protein deficiency very probably developed in these animals, but as there also would have been a deficiency of other factors, the experiments are difficult to interpret. The following study was undertaken to determine as directly as possible the effect of hypoproteinemia on the formation of bony callus following fractures in dogs.

METHOD

Medium-sized mongrel dogs were employed. These animals came from agricultural communities and appeared entirely normal at the beginning

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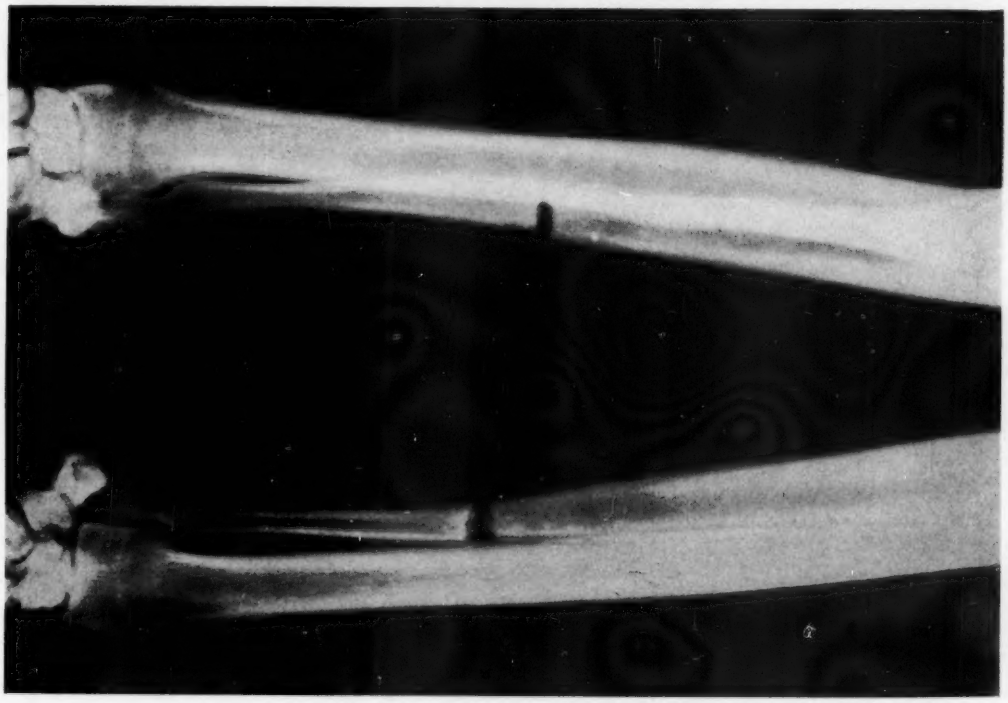
of the study. Hypoproteinemia was induced by a low-protein diet and repeated plasmapheresis. This method not only reduces the plasma protein concentration but depletes the labile protein reserve of the body as a whole. The diet was designed to be adequate for all of the animal's requirements except protein. It was made up as follows: carrots, 4.5 kg.; turnips, 4.5 kg.; rice, 2.0 kg.; oleomargarine, 1.6 kg.; cod-liver oil, 100 c.c.; bone ash, 50 Gm.; sodium chloride, 100 Gm.; yeast concentrate, 5 Gm.

A.



B.

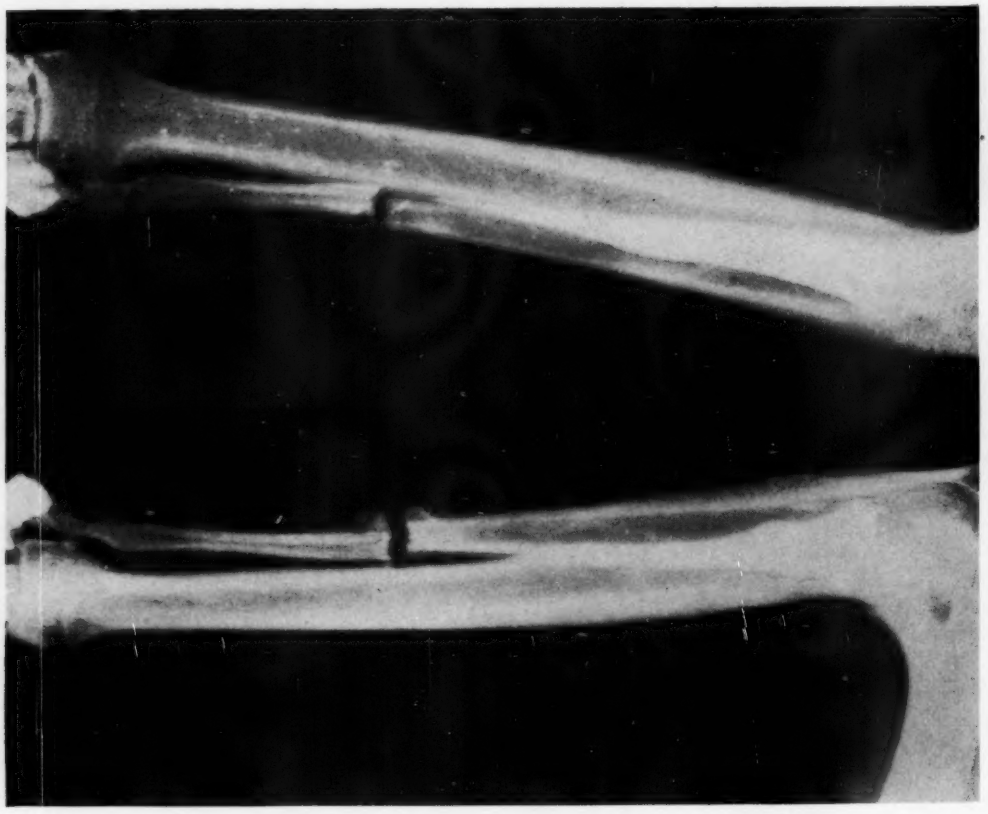
Fig. 2.—*A.* Roentgenogram of left foreleg of Dog 699 forty-five days after fracture of the ulna. The animal was hypoproteinemic during this period as shown in Fig. 1. *B.* Roentgenogram of right foreleg of Dog 699 thirty-nine days after fracture of the ulna. The plasma protein concentration had been restored to normal. There is a greater amount of callus visible by x-ray.

The carrots and turnips were coarsely ground and boiled for twenty minutes with the rice. The other ingredients were then added with the exception of the cod-liver oil and yeast, which were not added until the mixture had cooled. The stock food was carefully mixed and refrigerated. The protein content of the diet was approximately 1 per cent. The dogs were given as much as they desired every day.

Plasmapheresis was carried out by aspirating blood from the femoral artery into sterile 250 c.c. centrifuge bottles containing sufficient sodium citrate to prevent coagulation. After centrifugation the plasma was aspirated from the bottles and the cells diluted with normal saline solution and returned, usually within an hour, to the animal from which it had been taken. The bleeding was carried to the point of mild air hunger. It was usually possible to remove 350 to 400 c.c. of blood at

a time, and the procedure was carried out about three times per week until the serum protein level declined to below 4 Gm. per cent. Following this plasmapheresis was repeated often enough to maintain the protein concentration at about this level for a period of six weeks following fracture.

A.



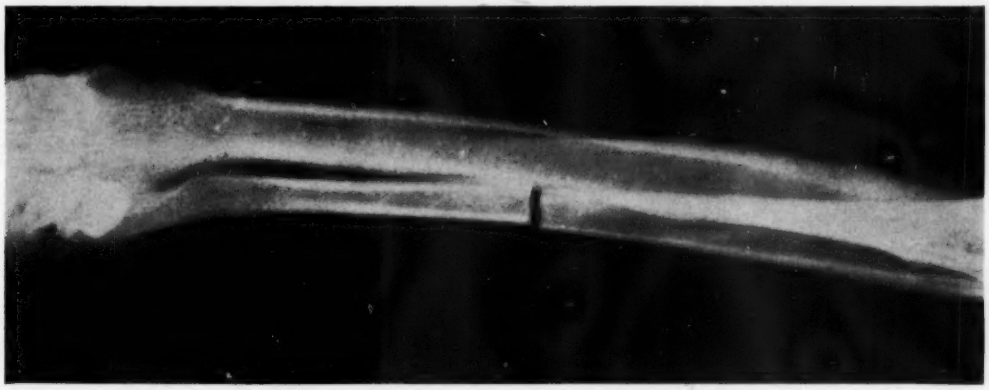
B.

Fig. 3.—*A.* Roentgenogram of left foreleg of Dog 700, forty days after fracture of the ulna. The animal was hypoproteinemic during this period as shown in Fig. 1. *B.* Roentgenogram of right foreleg of Dog 700 thirty-nine days after fracture of the ulna. The plasma protein concentration had been restored to normal and more callus is seen.

During the control periods the diet consisted of table scraps. Stock dogs subsisting on this diet maintain plasma protein concentrations of 6 to 7 Gm. per cent.

The type of fracture chosen for the study was Gigli saw section of the ulna. The advantages of this fracture for experimental work lie in the fact that the radius acts as a splint and that the position of the fragments, the direction of the line of fracture, and the degree of fixation all are relatively constant. The fracture is also readily accessible for x-ray examination. Furthermore, union occurs very slowly, probably on account of the separation of the fragments, so that callus formation can be studied over a considerable period. The separation of the fragments makes it somewhat easier than usual to study the development of bony callus roentgenographically.

Three dogs were rendered hypoproteinemic in the late spring of 1938 and the left ulna of each animal was sectioned about two inches above the distal end. All the wounds healed per primam. The plasma protein concentrations of these animals are shown in Fig. 1. After a period of six weeks the hypoproteinemic regime was ended. One of the animals died during the summer but the other two made a complete recovery and were used as controls in 1939. At this time their serum protein



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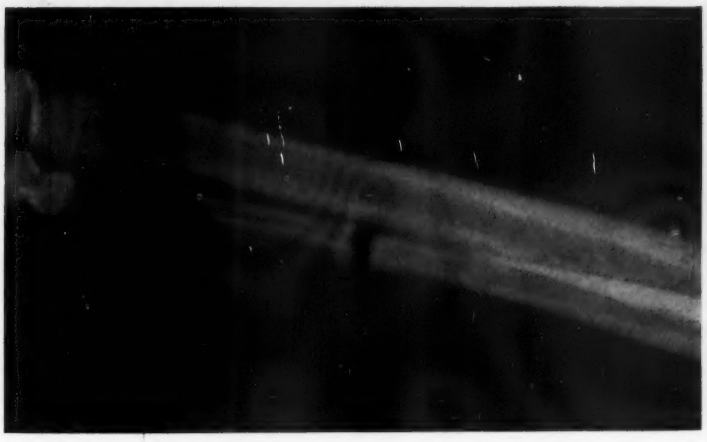


B.

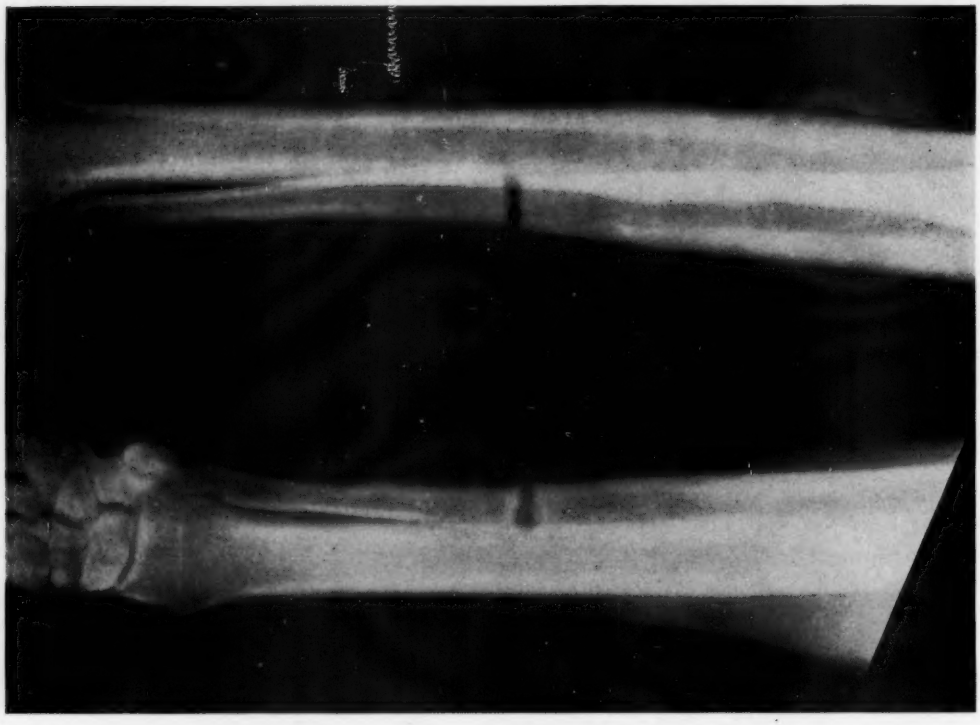
Fig. 4.—*A.* Roentgenogram of the foreleg of Dog 697 forty days after fracture of the ulna. The animal was hypoproteinemic during this period as shown in Fig. 1. *B.* Roentgenogram of the foreleg of Dog 904 forty days after fracture of the ulna. The plasma protein concentration was normal.

levels were within the normal range and Gigli saw section of the right ulna was carried out at approximately the same level. Later another normal dog was used for the third control. The x-ray evidence of callus formation at forty to forty-five days in the hypoproteinemic dog is compared with that seen after about the same interval in the normal dog (Figs. 2, 3, and 4). A later comparison showing the callus formation in the hypoproteinemic dogs at sixty to seventy-four days as compared with that in the control fractures at about sixty days is shown in Figs. 5, 6, and 7.

The fact that callus proliferation was so much more abundant in Dog 700 than in Dog 699 is probably due to a difference in age which was not realized at the beginning of the experiment. Dog 699 appeared to be rather an old animal; whereas, Dog 700 had not attained its full growth when the experiment began. Both of the other dogs appeared to be mature but not old. However, their actual ages were not known.

In all six comparisons it will be seen that less callus formation occurred when the animals were hypoproteinemic.

A.



B.

Fig. 5.—*A.* Roentgenogram of the left foreleg of Dog 699 seventy-four days after the fracture. Although the protein depleting regime had been stopped, callus is still not visible. *B.* Roentgenogram of the right foreleg of Dog 699 sixty-three days after fracture. A faint zone of callus is visible which almost bridges the gap between the ends of the ulna.

DISCUSSION

Many factors have been studied in connection with fracture healing. Some of these appear quite basic such as calcium metabolism, and the influence of vitamin D, while others are more obscure, such as vitamin E and orchidectomy. Vitamin C has also been studied in this connection, but the role of the plasma proteins has not received much attention in recent years.

Proteins are seldom thought of in connection with bones yet like all living tissues the bones undoubtedly require protein for growth. Furthermore, the first phase of fracture healing appears to consist in the formation of granulation tissue between the fragments. Here fibroplasia plays a role and severe hypoproteinemia has been shown to retard this process seriously.

The circulation of the hypoproteinemic animal may be considerably altered. Whipple and his associates have noted a marked decrease in plasma volume in their plasma-depleted animals. It is well known that a large fraction of the serum calcium is bound to the serum protein so that when serum protein concentration is low, serum calcium concentration is also reduced. It is not possible at the present time to state by what mechanism the hypoproteinemic state interfered with the formation of bony callus. It is important always to keep in mind that hypoproteinemia is not an abnormality that exists alone but one which is associated with many physiologic alterations.

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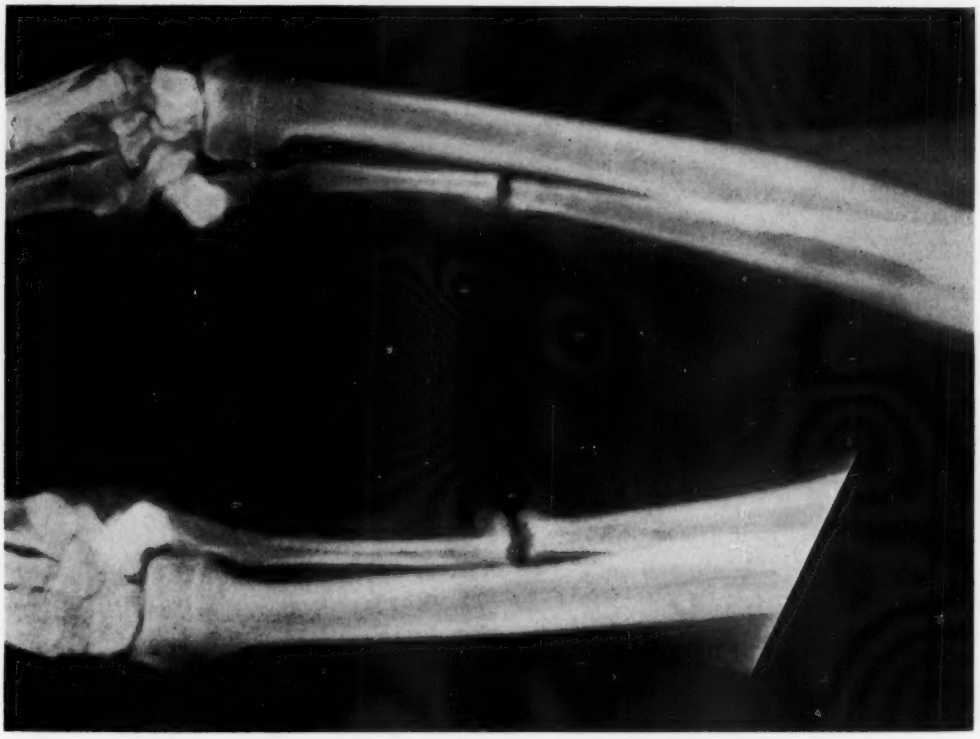


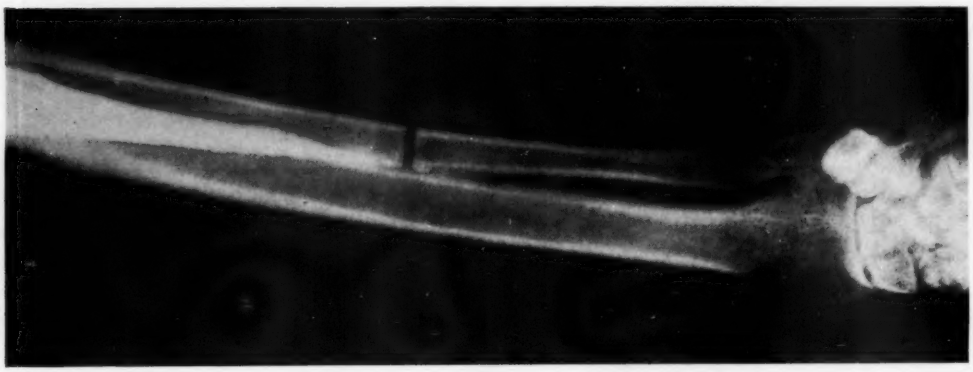
B.

Fig. 6.—*A.* Roentgenogram of left foreleg of Dog 700 sixty-four days after fracture showing some callus formation. The protein depleting regime had been stopped, but callus formation is still retarded as compared with that seen in Fig. 6*B*. *B.* Roentgenogram of right foreleg of Dog 700 sixty-three days after fracture. The plasma protein concentration was normal throughout this experiment.

The differences noted in these animals were consistent not only in the roentgenograms shown but in others taken at intervening periods. The use of two of the three hypoproteinemic animals as their own controls tends to eliminate the influence of unknown constitutional and individual factors. It should be noted that these two animals were almost a year younger at the time of the hypoproteinemic phase than at the time of the control fracture so that in so far as age is a factor it should have diminished the effect observed.

Hypoproteinemia has not been observed clinically by us as a cause of delayed union. Other factors induce such wide variations in the rate of

fracture repair in patients that it seems doubtful whether opportunity for an adequate evaluation of the role of hypoproteinemia in fracture healing in patients will be available to any one clinic unless in certain parts of the world food shortage should cause an epidemic of hypoproteinemia.



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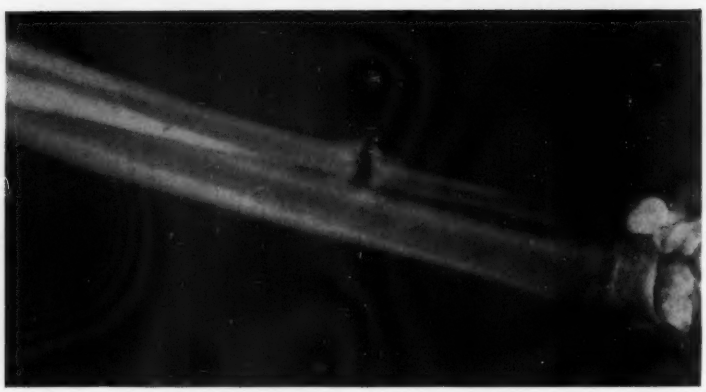

B.

Fig. 7.—*A.* Roentgenogram of foreleg of Dog 697 sixty days after fracture. Hypoproteinemia had been maintained until shortly before this examination was made. *B.* Roentgenogram of foreleg of Dog 904 sixty-one days after fracture. The plasma protein concentration was normal.

CONCLUSION

Experimental data are presented indicating that severe hypoproteinemia retards the formation of bony callus in fractures produced in dogs by section of the ulna with a Gigli saw.

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SECONDARY OR POSTOPERATIVE PAROTITIS

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ALTHOUGH parotitis is a rare postoperative complication, it does occur with sufficient frequency to justify the interest of every physician. Numerous theories have been advanced concerning the etiologic factors in this condition, chief of which are (1) degeneration of the parotid gland as a result of high fever, (2) degeneration of the parotid gland attributable to surgical procedures on the generative system, (3) the toxin theory, (4) involvement of the gland by infected emboli from the operative site, (5) infection extending through the lymphatics from an adjacent inflammatory process, and (6) ascending infection of the parotid gland by way of Stensen's duct.

It is the consensus today that the theory of ascending infection is the one most tenable. Berndt, Buck, and Buxton[1] carried out some interesting experimental work, in which they demonstrated the ease with which the parotid gland may become infected through the duct as compared with the hematogenous route. Seifert[2] also called attention to the infrequent appearance of suppurative parotitis in cases of staphylococcic septicemia.

The clinical picture of secondary parotitis usually is clear-cut and the diagnosis is made easily. Onset occurs most often between the first and fifth postoperative days, but it may occur at any time. It is associated with fever, swelling over the parotid gland, and in all cases some degree of discomfort which is most marked on opening and closing of the jaw. On examination, the orifice of Stensen's duct usually is visibly inflamed. Besides the redness and swelling about the orifice, turbid saliva or pus may be expressed by gently massaging along the course of the duct. This is not necessary to make the diagnosis and is a practice which probably should be condemned because of the added discomfort to the patient. Rarely is the seventh cranial nerve involved and then only when suppuration is present.

There seems to be an almost universal misunderstanding as to the severity of this condition. In fatal cases the course often is rapid, but almost without exception this is due to other pathologic processes within the body. If death occurs, parotitis usually is not more than a contributory cause and in many cases has disappeared completely before death. The generally held belief that parotitis is a local process produced by an ascending infection through Stensen's duct makes it hardly understandable that it could have the high mortality rate so frequently attributed to it. Green[3] found that mortality rates in individual reports in the literature ranged from 25 to 60 per cent. Pearson[4] quoted the

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combined American statistics as indicating a mortality rate of 58 per cent, with an incidence of the disease of 1 case in 2,275 cases in which operations were performed. Blair and Padgett[5] gave a mortality rate of 50 per cent in their cases. Rankin and Palmer[6] in a review of 79 cases collected from the literature found a mortality rate of 46 per cent; Bowing and one of us (R. E. F.)[7] found a mortality of 6 per cent. Talbot[8] was one of the first to call attention to the overemphasis which has been placed on the excessive mortality rates attributed to postoperative parotitis.

Our study consisted of 190 cases of postoperative parotitis; in 81 conservative measures were employed and in 109 cases radiation therapy. In this series 1 death could be attributed directly to the parotitis, a mortality rate of less than 1 per cent. The condition was associated most frequently with operations which involved the colon, pelvis, biliary tract, and stomach in that order.

We wish to stress the low mortality rate associated with this condition, although active treatment is indicated when the complication is first noted. In 7 of 18 cases in our series in which death occurred there was some evidence of parotitis at the time of death. In all but 1 of these 7 cases the coexisting pathologic processes were of such a nature that it is hard to conceive that parotitis played more than a contributory part as a cause of death. Because of the low mortality rate associated with parotitis we have omitted intentionally any comparison of figures on the number of deaths of patients treated with radium as compared to those treated by conservative measures.

If parotitis does not have a high mortality rate, then morbidity is the next most important consideration. When surgical drainage of the parotid gland becomes necessary, it adds to the necessary period of hospitalization and to the expense of the patient. From this standpoint radiation therapy seems to have a definite place in the treatment of this complication, for suppuration occurred twice as often in the group treated by conservative measures.

If the hypothesis that ascending infection by way of Stensen's duct is most often responsible for postoperative parotitis is accepted, then it seems rational that all prophylactic treatment should be directed to the mouth. This should include the avoidance of dehydration of the patient and careful hygiene of the mouth. Every effort should be made to stimulate the secretion of saliva by the use of chewing gum, slices of lemon and orange, or candy, and the avoidance of the use of those drugs which would tend to diminish the free flow of saliva.

Parotitis usually is treated by the conservative method or by irradiation. Operative intervention at present is reserved for those cases in which suppuration occurs. Conservative treatment consists of the application of warm packs or ice packs and the use of diathermy by the air-spaced method. Diathermy by this method consists of placing the unit 1 to 2 cm. from the involved parotid gland, thus avoiding contact with the involved tissue. One to two treatments are given daily for thirty minutes each. In addition to diathermy, hot or cold packs are

used in the intervening periods. It is best perhaps to use cold packs first; if there is evidence of suppuration, heat in the form of poultices is probably more efficacious in localizing the process. Leithauser and Cantor[9] recommended the use of massive doses of compound solution of iodine (Lugol's solution). Intravenous administration of mercurochrome was used previously, but of late this method has been largely abandoned because of failure of support of the early belief that mercurochrome had a specific effect on staphylococci.

The use of radium was recommended early by Rankin and Palmer and later by Bowing and one of us (R. E. F.). Of the two methods of radiation therapy, namely radium and roentgen rays, the latter is probably the method of choice as the length of treatment is shortened and the discomfort to the patient with the use of radium packs is obviated. It should be borne in mind that suppuration may not be evidenced by fluctuation because of the firm capsule which encases the gland. It is well, however, to wait until fluctuation is present before resorting to incision. If pus is suspected, aspiration may be of help in determining its presence. Numerous incisions have been recommended, but the Y-shaped incision as suggested by Fisher[10] is perhaps as satisfactory as any.

CONCLUSIONS

From study of our series of cases of postoperative parotitis, the following conclusions seem warranted.

1. Acute, secondary parotitis is a postoperative complication which is rarely seen.
2. The mortality rate associated with this condition is low, but if suppuration occurs, morbidity may be great.
3. The route of infection usually is by way of Stensen's duct.
4. Prophylactic treatment should be directed to the mouth.
5. Radiation therapy reduces the morbidity of this complication.
6. Surgical drainage rarely is indicated and then only in the presence of suppuration.

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THE INFLUENCE OF CALORIC RESTRICTION UPON THE INCIDENCE OF SPONTANEOUS MAMMARY CARCINOMA IN MICE

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INTRODUCTION

THE possibility that dietary factors play a role in determining susceptibility to cancer has long been recognized. A survey of the literature made in this laboratory revealed about 350 papers bearing upon the problem. This extensive literature cannot be reviewed here. In general it can be said that to our knowledge there is no previous study in which the incidence of spontaneous malignancy has been observed in relation to variations in simple caloric intake, when the ingestion of the known dietary essentials (minerals, vitamins, and amino acids) has been held constant. A number of workers have studied the effects of restriction of total food intake upon cancer incidence. The first suggestive studies of this type in relation to incidence of spontaneous mammary carcinoma in mice are those of Sivertsen and Hastings (1938). Their deduction that reduction in total food intake decreases the incidence was confirmed by Tannenbaum (1940). These observers have presented evidence to show that reduction in amount of all food elements results in a decreased incidence of spontaneous mammary carcinoma in mice.

It appeared to us that no satisfactory solution of the problem of the influence of diet upon cancer incidence was possible unless the effects of alterations of individual factors in the diet were studied separately. We have therefore begun such a detailed analysis with an investigation of the incidence of mammary carcinoma in the C_3H strain of mice in relation to the calorie content of the diet, holding all other known dietary essentials as nearly constant as possible. Mice of the C_3H strain were employed because they show a high cancer incidence in the virgin state, and our experience with A strain animals indicated that a caloric restriction greatly reduced fertility.

METHODS

The C_3H mice employed in this study were obtained from the Jackson Memorial Laboratories, Bar Harbor, Maine, and were certified to

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be a pure strain, selected for high cancer incidence. The mice were individually caged in galvanized iron cages, partly wire mesh and partly sheet. They were fed once a day in nonspill cups made from ointment tins, the covers of which were cut to admit the head of a mouse. The proper amounts of the restricted diet, fed at different ages, were measured by putting the food into hollowed-out brass molds, cut to hold the desired quantity by weight. The diet was put into the mold, scraped off evenly, then tapped out into the food cup. A wire mesh disk inserted above the food prevented spillage from both the restricted and *ad libitum* feeders. Tap water was continuously available. The animals were housed from the age of 1 month in a room with the temperature controlled at 80° ± 2° F., and the relative humidity at 45 ± 15 per cent saturation. The animals were identified by ear tattoo. Weights were recorded weekly at which time careful inspection and palpation were made for discovery of tumors. Tumorous animals were sometimes allowed to die spontaneously but were usually sacrificed under ether after the masses had become large. A complete examination was made of the entire mammary region in animals dying of whatever cause. The lungs and liver were also examined carefully, but other organs have not been studied consistently. Any tissue presenting an abnormal appearance at autopsy was preserved, and portions were sectioned, stained, and studied microscopically.

The control mice were fed the diet indicated below in unrestricted amount. Food was kept before the animals at all times and the amount ingested measured by weighing. The restricted mice were fed an amount of protein, vitamins, and minerals approximately equal to that actually ingested by mice eating the control diet *ad libitum*, but the amounts of carbohydrates and fat fed were reduced so as to decrease the total caloric intake by about one-third. It should be re-emphasized that each mouse was fed individually a measured amount of food.

TABLE I*

COMPONENT	CONTROL DIET GM./100	RESTRICTED DIET GM./100
Glucose	33	22.0
Lard	20	15.3
Casein	28	37.4
Dry yeast (Anheuser-Busch Strain G7)	8	10.6
Dry alfalfa leaf	4	5.4
Salt mixture†	7	9.3

*Each animal was given a supplement of 0.1 c.c. of U. S. P. XI cod-liver oil and the same amount of wheat germ oil each week added directly to the food cup.

†$CaCO_3$-543, $MgCO_3$-25, $MgSO_4$-16, NaCl-69, KCl-112, KH_2PO_4-212, $FePO_4$-21, KI-0.08.

The composition of the diets employed was as indicated in Table I.

The composition of the restricted diet was calculated on the basis of observations on the food intake of control animals at various ages. The

amounts of food eaten by the *ad libitum* controls studied initially and the food allowed the restricted mice at various ages are indicated in Table II.

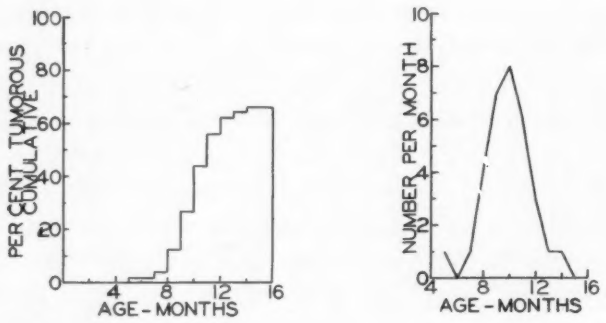
TABLE II

FOOD INTAKE

AGE (DAYS)	CONTROLS GM./MOUSE	RESTRICTED MICE GM./MOUSE
30- 35	1.6	1.20
36- 50	1.8	1.36
51-100	2.0	1.51
101-	2.3	1.74

It will be noted from Table I that 0.75 Gm. of restricted diet contains as much casein, yeast, alfalfa, and salt as 1.0 Gm. of the *ad libitum* diet.

Mice of nearly identical ages were used for the entire study and were divided into the two groups by pairing animals of equal weight at the start of the experiment.



A. *B.*

Fig. 1.—*A.* Spontaneous mammary carcinoma incidence of virgin female C_3H strain mice on the *ad libitum* diet, cumulative over sixteen months of age. *B.* Frequency of occurrence in relation to age of cancer incidence in the mice described in *A*.

RESULTS

A. *Cancer Incidence and Mortality.*—The times of occurrence of spontaneous mammary tumors proved at autopsy to be carcinoma, and the ages at death of C_3H virgin female mice on *ad libitum* as compared with calorie restricted diets are presented in Table III. It will be noted that at sixteen months of age no tumors have appeared in the restricted diet mice. At the same age 67 per cent of the animals fed *ad libitum* have developed histologically verified mammary carcinoma. At sixteen months 57 per cent of the restricted mice are still alive while only 29 per cent of the *ad libitum* animals survive. The distribution of cancer incidence with age in *ad libitum* fed mice is seen graphically in Fig. 1, *A* and *B*. The cumulative incidence is shown in Fig. 1*A* and the frequency of occurrence during each age month is shown in Fig. 1*B*. It

TABLE III

TUMOR INCIDENCE AND DEATH RATES IN C_3H STRAIN VIRGIN MICE ON CALORIE-RESTRICTED AND AD LIBITUM DIETS

MONTHS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
No. restricted living	44	44	44	44	44	44	42	40	39	38	34	34	28	27	27	25
No. restricted dying	0	0	0	0	0	0	2	2	1	1	4	0	6	1	0	2
No. restricted tumors	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
No. *ad libitum* living	51	51	49	49	48	48	46	42	35	27	21	17	16	15	15	15
No. *ad libitum* dying	1	0	2	0	1	0	2	4	7	8	6	4	1	1	0	0
No. *ad libitum* tumors	0	0	0	0	1	0	1	4	7	8	6	3	1	1	0	0
No. *ad libitum* tumors cumulative	0	0	0	0	1	1	2	6	13	21	27	30	31	32	32	32
Percentage tumors *ad libitum*	0	0	0	0	2.04	2.04	4.16	12.5	27.2	43.8	56.3	62.5	64.6	66.6	66.6	66.6

will be seen that tumors first appeared in the fifth month and that the maximum frequency of appearance occurred during the tenth month of life.

Since 57 per cent of the restricted animals are alive at the sixteenth month, it is premature to speculate as to the eventual fate of these animals with respect to cancer incidence; however, they have survived six months, or about one-third of the normal life span, beyond the time of maximum cancer incidence in their controls without the appearance of tumors in any animal. Furthermore this has occurred on a diet which has increased the life span significantly. The differences in the mortality experience in the two groups are shown graphically in Fig. 2.

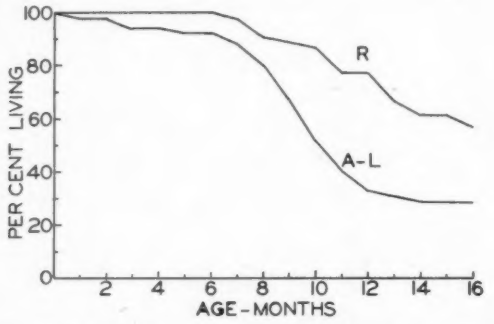


Fig. 2.—The percentage of C3H virgin female mice living at various ages. Curve A-L presents the values for the *ad libitum* diet; Curve R for the restricted diet.

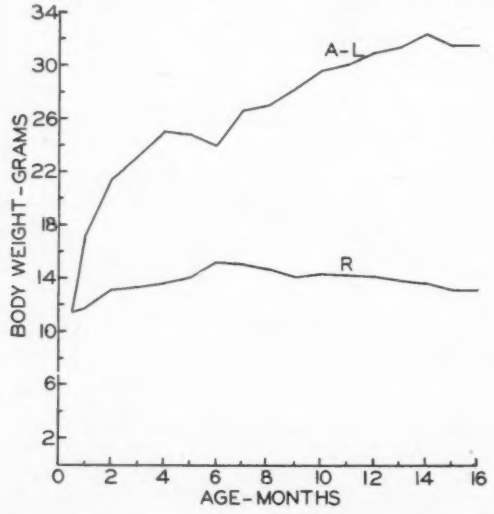


Fig. 3.—Mean body weights in relation to age of C3H virgin female mice. Curve A-L presents the values for the *ad libitum* diet; Curve R for the restricted diet.

It is reasonable to conclude from these data that a caloric dietary restriction which has improved the longevity of C_3H female virgin mice has also reduced mammary cancer incidence at sixteen months from a control value of 67 per cent to zero in a significantly large series of animals. Mammary tumors may still occur at older ages in these mice

but eleven months have elapsed since the occurrence of the first tumor in the control series without tumor development in the restricted animals. This period is already nearly two-thirds of the usual life span.

B. *Growth.*—The mean body weights over time for the two groups of mice are shown in Fig. 3. The caloric restriction resulted in sharp limitation of weight increase. There is little or no visible fat in the restricted-diet mice. It is worthy of mention that the restricted-diet animals were much more active than the *ad libitum* group. The additional energy cost of exercise decreased the amounts of fat and carbohydrate available for body growth in the restricted animals and was therefore partly responsible for the low body weight. It is also interesting in this connection that a group of subline A strain mice maintained on the same restricted diet showed at age twelve months an average body weight 4 Gm. greater than did the C_3H mice. The two strains showed identical mean body weights on *ad libitum* feeding. Obviously the two strains respond somewhat differently to dietary caloric restriction.

DISCUSSION

The reduction of spontaneous mammary carcinoma at age sixteen months from an incidence of 67 per cent in C_3H virgins on *ad libitum* feeding to zero on a diet adequate in protein, vitamins, and minerals, which has been observed in this study, appears to prove that simple caloric restriction can greatly reduce the frequency of cancer during the usual period of maximum incidence. In all previous work caloric restriction has been complicated by simultaneous reduction in protein, vitamin, and salt intake, since the diets employed were identical in composition but different in amount in the full-fed and restricted groups. In such studies the reasonable possibility existed that a decrease in cancer incidence following food restriction was due to protein and vitamin deficiency rather than to caloric restriction. Furthermore, in no previous study have mice been caged individually and actual food intake of each animal controlled. When groups of mice are caged together, the more aggressive animals will obtain proportionately more food. Moreover, in previous studies on the effects of dietary restriction on spontaneous cancer incidence, commercially prepared animal feeds have been employed as part or all of the diets. Since their composition is uncontrollable, it seems advantageous to employ materials of known composition. The *ad libitum* diet used in this study gave appreciably more rapid growth than was obtained with purina fox chow.

The mechanism by which simple caloric restriction reduces spontaneous mammary cancer incidence is still obscure. Three known factors influence mammary cancer frequency in mice: (1) genetic susceptibility, (2) endocrine influence, and (3) milk factor (for literature see Snell, 1941, and Bittner, 1940). Factors 1 and 3 are known to be

present in the mice employed in this study. The adequacy of Factor 2, the endocrine influence, is uncertain under the conditions employed. The C_3H strain was employed in this study after an attempt had been made to use A strain mice. The A strain shows high cancer incidence only in multiparous females. It was found that the restricted diet females were relatively infertile and only 37 per cent became pregnant, usually only once, on repeated exposure to males of known potency. None of these females became cancerous, a result which lends corroboration to the conclusion drawn from the present study. Nevertheless the result was unsatisfactory because the hormone factor had obviously not been controlled. The A strain females which were sterile while on the calorie-restricted diet became normally fertile within a few days after being placed on *ad libitum* feeding. There were, therefore, no irreversible changes produced by caloric restriction.

In the C_3H strain the incidence of cancer is the same in virgin and parous females. This fact does not exclude the importance of a hormone influence. Nevertheless if such a factor exists it is supplied by the endocrine organs, presumably the ovaries, independent of pregnancy. It is possible that caloric restriction either decreases the production, increases the rate of destruction, or increases the threshold of sensitivity of breast tissue to the hormone involved. The evidence available at this time does not permit a final conclusion as to whether one of these changes actually occurs. However, studies are now under way designed to determine whether castrates given estrogenic materials parenterally show altered cancer incidence on restricted as compared with *ad libitum* diets, and also to ascertain the dose of estrogenic material necessary to maintain estrus on the two diets. Regarding the latter it can be said that no difference is apparent between the two groups as to sensitivity to estrogen.

Further studies on dietary restriction have been started in order to ascertain, among other facts, the latest period in the life span at which the institution of caloric reduction can significantly lower spontaneous cancer incidence. It is fully recognized that the degree and the time of diet restriction necessary to accomplish reduced cancer incidence are important questions in connection with the general problem, and especially in connection with any bearing which the results of animal experimentation may have upon the human cancer problem.

CONCLUSIONS

1. The incidence of spontaneous mammary carcinoma in C_3H strain virgin female mice has been determined in relation to the calorie content of the diet, with the protein, vitamin, and salt intake approximately constant.

2. Restriction of carbohydrate and fat intake to accomplish a reduction of approximately one-third in total calories ingested resulted

in a change in mammary carcinoma incidence from 67 per cent in sixteen months in the controls to zero in the calorie-restricted mice.

3. The life span of the calorie-restricted mice was considerably increased over that of the fully fed controls.

4. Factors of possible importance in connection with these findings have been discussed.

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EXPERIMENTAL STUDIES ON ALIMENTARY AZOTEMIA

III. Site of Blood Absorption*

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THE syndrome of alimentary azotemia and evidence concerning its mechanism have been presented by us in previous publications.[1, 2, 3] These results were essentially in agreement with those of Sanguinetti[4] and Schiff and his co-workers.[5, 6] Strong evidence was offered in support of the following conclusions: (1) Alimentary azotemia occurs in cases of massive hemorrhage into the intestinal tract, and this in turn most often results from a bleeding peptic ulcer. (2) The degree of the azotemia is of considerable prognostic significance, high blood urea nitrogen values being associated with high mortality. This is probably because the increase in blood urea nitrogen is a measure of the amount of blood lost. (3) The azotemia is due to absorption of digested blood and especially of its erythrocyte fraction (and in turn the latter's contained hemoglobin). (4) Finally, that since marked rises in blood urea nitrogen were also obtained following ingestion of protein, it seems as though the rise is probably due to and to a large extent proportional to the absorption of protein from the gastrointestinal tract.

The foregoing experiments were performed on the basis of blood introduced by stomach tube into the stomachs of experimental animals, and hence dealt primarily with blood in the stomach. A search of the literature revealed only one mention concerning alimentary azotemia occurring after absorption elsewhere than from the stomach or duodenum, although in various diseases large amounts of blood are lost into the lower portions of the gastrointestinal tract.

The only observations on this aspect of the subject prior to our own are those of Schiff and his associates[6] in 1939 on human beings. These authors fed blood into the fasting stomach through a Rehfuss tube, and into the jejunum or upper ileum and colon through a Miller-Abbott tube. The maximum increase in the blood urea nitrogen was greater when the blood was introduced into the jejunum or upper ileum. After injection into the colon, no appreciable rise occurred. In clinical cases of bleeding into the colon, these authors observed no rise in the blood urea nitrogen.

Therefore it occurred to us to attempt to ascertain more precisely the site or sites in the gastrointestinal tract and ectopic sites, if any, in which after introduction of blood this phenomenon will occur.

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*All of the experimental work was performed at the Henry Ford Hospital, Detroit, Mich.

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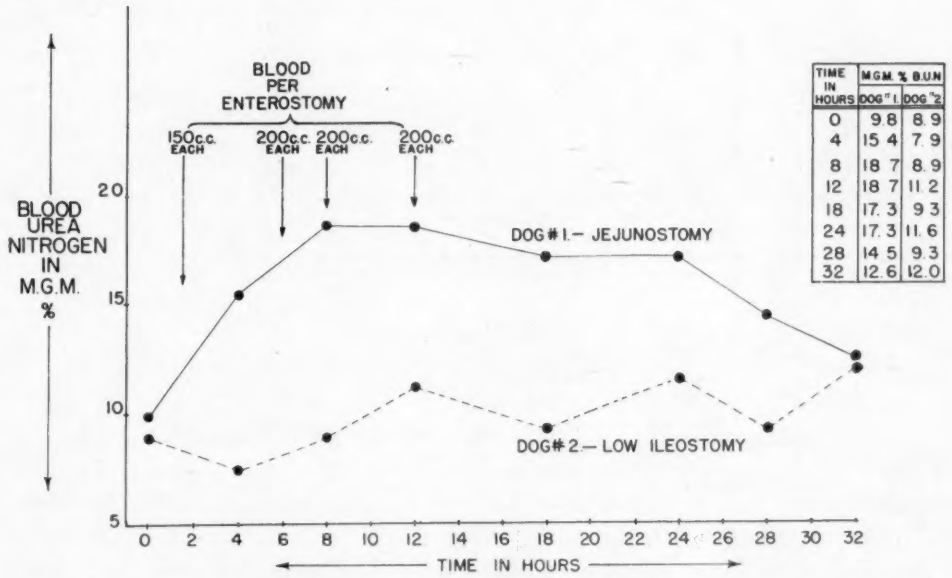
EXPERIMENTAL

Method.—Citrated whole beef blood and beef red blood cells were introduced in divided doses into the jejunum (two feet below Treitz' ligament) through a jejunostomy of the Maydl[7] type in two otherwise normal dogs. In a second set of two dogs, whole beef blood and beef red blood cells were introduced in divided doses low into the ileum (20 cm. proximal to the ileocecal valve), through an ileostomy of the Mann-Bollman[8] type. In additional experiments, one of the jejunostomy dogs and one of the low ileostomy dogs were given human red blood cells in a similar manner. In all, ten experiments were performed on four dogs.

Blood urea nitrogen determinations, using essentially the method of Van Slyke and Cullen[9] were made every four to six hours on each dog, from one to three days following the introduction of whole blood or of red blood cells by enterostomy into the respective levels of the small intestine. As in the previous experiments, the dogs were given their usual amount of food divided into four small meals daily. Water was given freely in the usual amounts. Daily hematocrit and hemoglobin determinations were made in six of the ten experiments revealing little change from the control level.



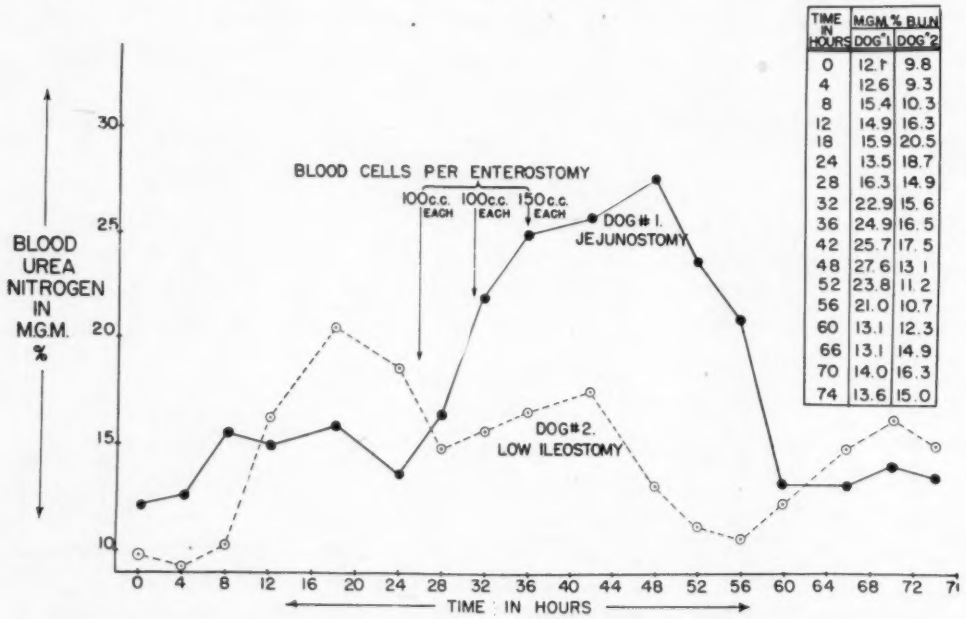
TIME IN HOURS	M.G.M. % B.U.N. DOG "1.	DOG "2.
0	9.8	8.9
4	15.4	7.9
8	18.7	8.9
12	18.7	11.2
18	17.3	9.3
24	17.3	11.6
28	14.5	9.3
32	12.6	12.0

Fig. 1.—The effect of blood in the production of alimentary azotemia at different levels of the gastrointestinal tract of dogs.

Results of Whole Blood Administration.—As shown in Fig. 1, it was found that within three hours following the first dose of blood given into the jejunum, a marked rise in blood urea nitrogen occurred and the level continued on an elevated plane, as long as blood was given at short intervals. There was a return to a normal level of blood urea nitrogen within twenty-four hours following the introduction of the last dose of blood. In marked contrast to this curve is shown the nonelevated blood

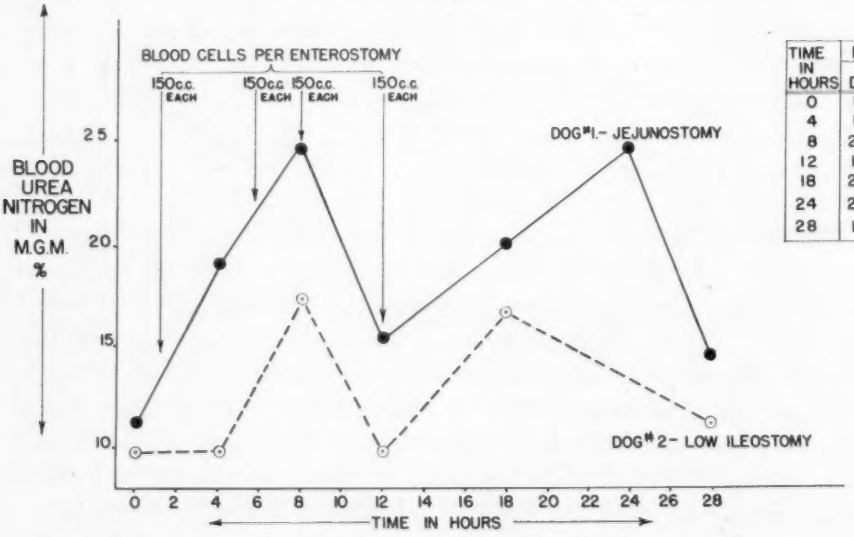
urea nitrogen curve of the dog receiving the same amounts of blood at the same intervals and time into the lower portion of the ileum. Azotemia could not be produced by giving as much as 750 c.c. of whole blood into the lower ileum.

Results of Blood Cells Administration.—In four experiments, two dogs were given washed beef red blood cells by jejunostomy in divided doses, and in a second set of two dogs beef red blood cells, in identical amounts and intervals, were introduced into low ileostomies.



TIME IN HOURS	M.G.M. % B.U.N. DOG "1	DOG "2
0	12.1	9.8
4	12.6	9.3
8	15.4	10.3
12	14.9	16.3
18	15.9	20.5
24	13.5	18.7
28	16.3	14.9
32	22.9	15.6
36	24.9	16.5
42	25.7	17.5
48	27.6	13.1
52	23.8	11.2
56	21.0	10.7
60	13.1	12.3
66	13.1	14.9
70	14.0	16.3
74	13.6	15.0

Fig. 2.—The effect of blood cells in the production of alimentary azotemia at different levels of the gastrointestinal tract of dogs.



TIME IN HOURS	M.G.M. % B.U.N. DOG "1	DOG "2
0	11.2	9.8
4	19.1	9.8
8	24.8	17.3
12	15.4	9.8
18	20.5	16.8
24	24.8	—
28	14.6	11.2

Fig. 3.—The effect of blood cells in the production of alimentary azotemia at different levels of the gastrointestinal tract of dogs.

As shown in Figs. 2 and 3, one of the animals receiving blood cells into the jejunum showed an initial elevation of blood urea nitrogen after one to two hours. Fig. 2 reveals the same type of curve in the jejunostomy animal as that for the animals following gastric ingestion of blood as previously reported.[1, 2, 3] However, it is to be noted that while the azotemia curves are of the same type, the degree of azotemia, though definitely abnormal, is possibly of a lesser degree for the same dosage of blood.

TABLE I

EFFECT OF BLOOD CELLS WHEN GIVEN AT DIFFERENT LEVELS OF GASTROINTESTINAL TRACT ON PRODUCTION OF ALIMENTARY AZOTEMIA IN DOGS

TIME IN HR.	MG. % BLOOD UREA NITROGEN	
	DOG 1 JEJUNOSTOMY	DOG 2 LOW ILEOSTOMY
0	11.2	9.8
1	Give each dog 150 c.c. blood cells per enterostomy	
4	19.1	9.8
6	Give each dog 150 c.c. blood cells per enterostomy	
8	Give each dog 150 c.c. blood cells per enterostomy	
8	24.8	17.3
12	Give each dog 150 c.c. blood cells per enterostomy	
12	15.4	9.8
18	20.5	16.8
24	24.8	–
28	14.6	11.2

In another experiment (Table I), the initial elevation of the blood urea nitrogen, in the jejunostomy animal, is to be noted, but this was followed by a fall to normal values in twelve hours followed by a second elevated peak in twenty-four hours, and a final return to normal four hours later. This drop of the twelve-hour reading is unexplained. In general, however, the results shown in Table I parallel those shown in Figs. 1 and 2.

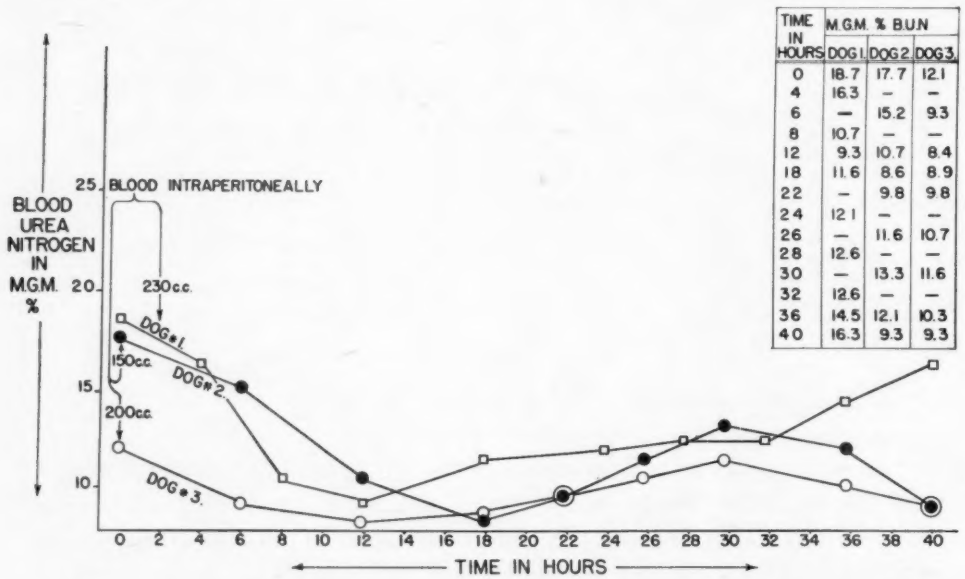
Additional experiments were performed as follows: One of the ileostomy dogs was checked two months later and despite the administration of 600 c.c. beef red blood cells, no increase in blood urea nitrogen occurred. This same low ileostomy dog was also given human red blood cells on two occasions. In the first experiment, 500 c.c. human red blood cells given by ileostomy produced no effect. In the second experiment, after administration of 600 c.c. of human red blood cells by ileostomy the blood urea nitrogen rose from 14 to 24 mg. per cent. It was then found that this dog had received a single large feeding of meat just before this rise occurred which may have been a causative factor. One of the two jejunostomy dogs was given 600 c.c. human red blood cells into the jejunostomy with a resultant rise in the blood urea nitrogen level of from 8.5 to 25.7 mg. per cent.

Results of Administration of Whole Blood Intraperitoneally.—Three normal dogs were given respectively, 150 c.c., 200 c.c., 230 c.c. of citrated whole blood intraperitoneally, using aseptic technique. Blood urea nitrogen determinations were made every four to six hours for forty-

five hours following the introduction of blood. In Fig. 4 are seen the graphs of the three flat curves for these animals. No elevations of blood urea nitrogen above normal values were found throughout these experiments.

SUMMARY

The administration of whole blood high into the jejunum of a dog produced an elevation of blood urea nitrogen with a return to normal levels in thirty-two hours, while the administration of identical amounts of whole blood low into the ileum caused no elevation of blood urea nitrogen.



TIME IN HOURS	M.G.M. % B.U.N.		
	DOG 1	DOG 2	DOG 3
0	18.7	17.7	12.1
4	16.3	–	–
6	–	15.2	9.3
8	10.7	–	–
12	9.3	10.7	8.4
18	11.6	8.6	8.9
22	–	9.8	9.8
24	12.1	–	–
26	–	11.6	10.7
28	12.6	–	–
30	–	13.3	11.6
32	12.6	–	–
36	14.5	12.1	10.3
40	16.3	9.3	9.3

Fig. 4.—No azotemia is shown following administration of blood intraperitoneally in dogs.

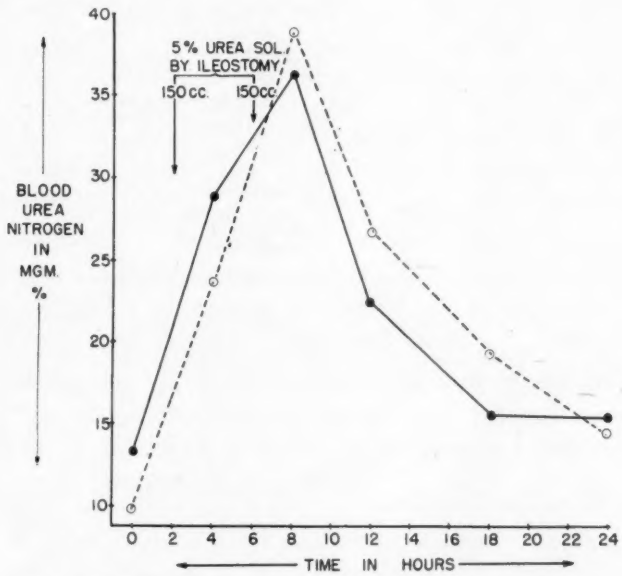
Two dogs were given blood cells high into the jejunum with resulting azotemia for periods of twenty-seven and thirty-four hours respectively. Two dogs were given identical amounts of blood cells low into the ileum without a resultant elevation of the blood urea nitrogen.

Three experiments were performed in which three dogs were given whole blood intraperitoneally without producing azotemia in the succeeding forty hours.

Correlation of these results with those previously reported showing that azotemia results from the intragastric administration of blood would indicate that to produce alimentary azotemia, blood must be present in the upper half of the alimentary tract. This conclusion, in turn, is capable of two interpretations: (1) that unless the blood is present in the upper portion of the intestinal tract, it is not absorbed in sufficient quantities to produce alimentary azotemia; or (2) that the blood must be digested in the upper portion of the gut to produce substances which, when absorbed, will produce alimentary azotemia.

Our results cannot give a conclusive answer as to which of these conclusions is more correct. We were, however, able to show that a 5 per cent urea solution produced as marked a rise in blood urea nitrogen when introduced into the stoma of one of our low ileostomy dogs as when introduced into one of the jejunostomy dogs. These results are shown in Fig. 5. Other experiments with predigested blood or red blood cells might have given the same or another result, but they were not performed.

At any rate, our experiments indicate that an appreciable alimentary azotemia results only when blood is present in the upper intestinal tract. This observation has an especial clinical application to cases of intestinal hemorrhage.



TIME IN HOURS	MGM. % B.U.N.	
	HIGH ILEOSTOMY	LOW ILEOSTOMY
0	13.3	9.8
4	29.0	23.6
8	36.2	38.8
12	22.4	26.6
18	15.4	19.3
24	15.4	14.5

Fig. 5.—The comparative effects of a 5 per cent urea solution in the production of alimentary azotemia in high and low ileostomy dogs. The solid line represents the results in the dog with a high jejunostomy, while the broken line represents the results in the dog with a low ileostomy.

CONCLUSIONS

1. Alimentary azotemia occurs in the experimental animal (dog) following the intrajejunal administration of whole blood or red blood cells. The degree of azotemia, although definite, is somewhat less than that produced by the intragastric administration of similar amounts of whole and blood cells.

2. Whole blood and blood cells introduced low into the ileum produce much less azotemia than when similar amounts are introduced higher up into the intestinal tract.

3. Whole blood in the peritoneal cavity of experimental animals (dogs) produces no azotemia.

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PILONIDAL SINUSES OCCURRING OVER THE HIGHER SPINAL SEGMENTS WITH REPORT OF A CASE INVOLVING THE SPINAL CORD

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PILONIDAL sinuses are rarely encountered over spinal segments higher than the sacrococcygeal region. A review of the literature reveals only thirteen cases previously reported. These usually revealed a sinus communicating between the skin surface and the meninges, but in no case was the lesion found actually to invade the substance of the spinal cord. In the case about to be presented, the lesion was shown at operation to be intramedullary. The mouth of the sinus presented itself over the upper margin of the third thoracic vertebra.

The lesions, as found over the higher spinal segments, present a microscopic pathologic picture quite identical with that of pilonidal sinuses occurring in the sacrococcygeal region. Clinically, however, the former are more serious because of their location over the spinal cord and its coverings. In this location, any infection of these sinuses is prone to be carried to the meninges. Furthermore, even in the absence of infection, sufficient pressure may be exerted by the lesion to produce compression of the cord elements and result in signs and symptoms typical of a cord tumor. The early recognition of this lesion at any level of the spine is essential to proper treatment. Surgical removal carries an excellent prognosis.

REVIEW OF LITERATURE

In Fig. 1 is shown the site of the unusually located pilonidal sinuses of the present case and those collected from the literature. An abstract of these cases is given as follows.

Clark[2] was the first to report a pilonidal sinus-like lesion occurring at a site away from the sacrococcygeal region. His case, a 13-year-old girl, had a small hair-containing sinus in the median line, between the spinous processes of the fourth and fifth cervical vertebrae. On examination she showed a lack of manual dexterity and an incapacity for work requiring finer movements of the fingers and hands. Roentgenograms were negative but for a demonstrable cleft in the arch of the third cervical vertebra. The lesion was not confirmed by either operation or necropsy.

Moise[11] reported the first proved case. His patient, a male aged 18 years, had a congenital discharging pilonidal sinus in the lower lumbar

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region. This became infected and produced a staphylococcus meningitis. At operation the sinus was found to extend through a bony defect at the junction of the first and second sacral vertebrae and to communicate with the subarachnoid space. A laminectomy was performed, the sinus and its granulation tissue excised, and the wound drained. The patient then went on to an uneventful and complete recovery.

Ripley and Thompson[13] reported quite a similar case two years later in a 3½-month-old male infant, who developed a fatal staphylococcus meningitis secondary to infection of a congenital pilonidal sinus. At operation the sinus was found to pass into the sacral canal, in the region of the second sacral arch, which was found to be absent. The sac removed at operation was found to contain a hair and sebaceous material.

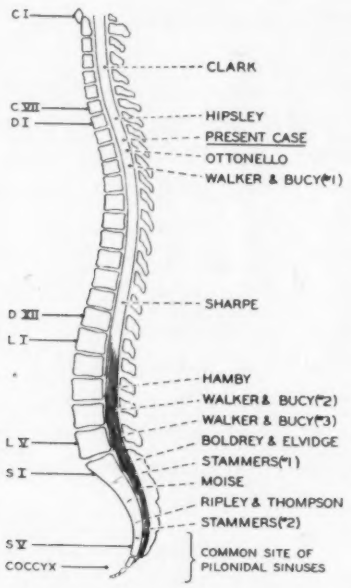

Fig. 1.—A diagram illustrating the higher spinal levels at which were found the pilonidal sinuses reported by the various authors.

W. Sharpe and N. Sharpe[14] reported a case of a male aged 3 years, with a congenital pinhead-sized depression over the lower thoracic region which drained purulent material intermittently. His back was rigid, and prior to operation he developed a spastic paralysis of both legs. Roentgenograms demonstrated a failure of fusion in the left lamina of the eleventh dorsal vertebra. At operation, a laminectomy was performed, and a fibrous mass containing hair and caseous material was removed from between the dura and the spinal cord. His convalescence was uneventful and the subsequent recovery nearly complete.

Ottonello[12] reported a case in a female, aged 20 years. She had a minute sinus over the third dorsal vertebra. Two weeks prior to hospital admission she developed a paraplegia, sensory symptoms, and a

vesicorectal incontinence. Roentgenograms revealed a rachischisis of the second thoracic vertebra, and a myelogram demonstrated a block at this level. At operation the sinus was found to communicate with a dermoid cyst which lay beneath the arachnoid. The cyst measured about 6.5 by 2 cm. and was filled with hair and sebaceous material. Following surgery the patient made a complete recovery but for a residual weakness of the lower extremities.

Hipsley[9] reported a case, a female, 3 years of age, who developed difficulty in walking four weeks prior to admission. She presented a discharging midline sinus over the first thoracic spine. This sinus was hair containing and the area about its orifice was indurated. The spinal fluid was xanthochromic, with 72 cells per cubic millimeter; lymphocytes, 80 per cent; neutrophiles, 20; no organisms. A myelogram showed an arrest of the lipiodal at the seventh cervical vertebra. . At operation the spine of the second dorsal vertebra was found to be bifid, and through a perforation at its base the sebaceous material of the cyst was seen to extrude. Lying subdurally and attached to the dura was a dermoid cyst, 18 by 12 mm., which was removed. Following surgery there was nearly a complete recovery.

Walker and Bucy[16] in an excellent article on congenital dermal sinuses stressed the fact that these sinuses extend to the meninges and that infection of such a lesion is prone to produce either a spinal meningitis or a subdural abscess. They presented three new cases. Their first case was that of a 5-year-old female, who developed symptoms at 6 months of age, and on whom a diagnosis of tuberculous meningitis was made at that time. This child, four and one-half years later, was found to have a congenital sinus over the fourth thoracic vertebra. Roentgenograms of this area showed an incomplete fusion of its laminae. At operation, the spinous process of this vertebra was found to be absent, and following a laminectomy, an inflammatory mass composed of numerous small sterile abscesses was excised from beneath the thickened dura. Postoperatively, the patient went on to an uneventful complete recovery. Their second case was a female, aged 3 years, with a similar lesion over the fourth lumbar vertebra, on whom a diagnosis of tuberculous meningitis had likewise been made. Roentgenograms showed an incomplete fusion of the laminae of the sacral segments, while the lumbar vertebrae were apparently normal. At operation, the sinus was seen passing between the fourth and fifth lumbar vertebrae down to the dura, to which it was firmly attached. Following laminectomy and incision of the dura, a small cystic cavity was encountered which was filled with thick, creamy pus, and some sebaceous material. The abscess extended from the level of the fifth lumbar inferiorly, to about the level of the twelfth thoracic vertebra superiorly, where a hole was noted in the floor of the abscess cavity. The wound was closed with drainage and her recovery was satisfactory.

The third case presented by Walker and Bucy was one operated upon some years previously by Dr. D. B. Phemister. The patient, a colored female, aged 3 years, presented a hairy pigmented area over the fifth lumbar spine, and in the center of this there was a minute sinus. Roentgenograms showed a failure of fusion of the spinous processes of the fifth lumbar and first sacral vertebrae. At operation, the sinus was found to pass through a defect in the spinous process of the fifth lumbar vertebra to a subdural inflammatory sac. This contained a few drops of glairy, gelatinous, slightly purulent material. The postoperative course was uneventful.

Hamby[7] reported a case exhibiting a pilonidal cyst, not communicating with the skin, associated with multiple other congenital abnormalities of the spine and cord. The patient, a white female, aged 20 years, was born with a midline dimple over the lumbar spine. About this a profuse growth of hair occurred in later years. She complained of back pain and difficulty in walking. Roentgenograms showed a failure of fusion of the laminae of the last three lumbar vertebrae, with an associated fusion of the bodies of the fourth and fifth. At operation, a tumor was exposed at about the level of the third and fourth lumbar vertebrae, which upon being incised revealed a sac containing fluid under pressure and a mass of curly hair. The deeper part of this pilonidal cyst was attached to a bony exostosis which arose from the anterior wall of the spinal canal. The spinal cord was seen to become bifid at this level and was noted to be longer than usual. Following operation with removal of the cyst, the patient made an uneventful recovery.

Stammers[15] reported two quite identical cases, in each of which the patient made an uninterrupted and apparently complete recovery following surgery. The first case was that of a male, aged 2 years, who developed symptoms six weeks prior to admission. He showed ease of fatigue, irritability, and difficulty in walking. Examination revealed a small sinus over the upper sacrum. From this sinus a fibrous cord could be felt running beneath the skin upward to the lumbosacral junction. This area was tender, and the spine was held rigid. Roentgenograms disclosed a spina bifida of the fifth lumbar vertebra. The spinal fluid was turbid, contained 426 cells (unspecified) per cubic millimeter, and showed numerous *Staphylococcus albus* organisms. At operation the sinus was found to communicate through the spina bifida with a large dermoid cyst lying within the spinal canal. The second case, a male aged 4 years, presented a discharging congenital sinus over the lower sacrum. Two weeks prior to admission, he began to complain of headaches and pain in the lower back, had vomited and shown a fever. Examination revealed a hyperextended spine, retracted head, neck rigidity, spasticity of the arms, and the knees drawn upward. There was a bilateral Kernig sign. Lumbar puncture produced "a few drops of thick ropy pus" from which "coliform bacilli and enterococci" were recovered. Repeated

cisterna puncture produced a sterile cerebrospinal fluid. At operation the sacral canal was explored and the cavity found to contain thick pus. The sinus was found to be attached to the dura mater of the cord.

Boldrey and Elvidge[1] have reported the most recent case. Their patient, a boy 2½ years of age, had a congenital sinus over the lumbosacral spine which had drained intermittently for nine months. For five months he had periodic attacks of chills, fever, opisthotonos and vomiting. On admission he held his knees drawn up and showed a neck stiffness. At operation the sinus was found to pass through a bifid fifth lumbar vertebra, and to communicate with an infected dermoid cyst lying subdurally. The cyst extended from the twelfth dorsal to the second sacral vertebra and was intimately adherent to many roots of the cauda equina. It contained sebaceous material, hair, and pus. Following a prolonged stormy convalescence the patient made a good recovery.

REPORT OF A CASE*

D. D. C., a white, male student, aged 19 years, entered the University Hospital, on May 7, 1936. His chief complaint was that of "difficulty in walking." He first developed symptoms thirteen years previously when he experienced a "limp" in his right leg while convalescing from an attack of measles. From May through August, 1923, the limp remained apparently stationary, and then a gradual improvement was noted. However, in November, following an attack of chicken pox, there was such a marked exacerbation of the symptoms that walking became an impossibility. Two months later, when he was again able to walk, the left foot began to trouble him for the first time. He was informed by his mother that he then walked with his legs crossed "like a pair of scissors," and that he had a marked "trembling of his feet" (probably a clonus).

The following April he entered a large metropolitan hospital for a thorough case study. Examination here revealed a dimple with a small tuft of hair in the region of the third dorsal spine. His mother stated she had noticed this dimple since early childhood. Roentgenograms of this region were taken and reported to be normal. Spinal fluid examination revealed 15 W.B.C. (unspecified) per cubic millimeter, 1+ globulin, and mastic 33100000. No definite diagnosis was made on two visits, however, and no specific therapy was instituted.

A gradual decrease in symptoms was noted during ensuing months, and after one year a fair recovery was made. There was then only a mild stiffness and some weakness of the legs, upon prolonged exercise. He was able to resume school life and take an active part in both basketball and football. Periodically the dimple over his spine produced soreness in the shoulder region and back. On one occasion the soreness was relieved when his mother extracted the hair. On a subsequent recurrence of this trouble, the mother removed the hair early to obviate further soreness, but this time it only served to aggravate the pain. Hair was removed from the dimple last about four years ago.

Two years prior to the present admission, following an outing at which he became very fatigued, there was a recurrence of the symptoms. This time the left foot was the first to become involved. The condition grew progressively worse until three months before admission when the right foot also became involved. This forced him to drop his college work, as he was able to walk only about twelve to fifteen feet

*This case is also referred to in a current publication by Dr. Carl List on "Dermoids of the Spinal Cord."

without resting his legs. His difficulty has been concerned primarily with locomotion, and he was entirely free from pain. Recently, however, he has become constipated and experienced some difficulty in initiating urination.

The past history revealed no other illnesses than those described above. The family history was significant only so far as it revealed a brother who had a "cyst removed from the end of the spine." This was diagnosed to be a pilonidal cyst.

Fig. 2.—Myelogram taken with the patient in a 60° Trendelenburg position. The iodized oil, which has been blocked at the level of the third dorsal vertebra, has a concave upper surface suggesting a cord tumor. There is a noticeable thinning of the pedicles in the left upper dorsal region, when compared with those on the right.

Physical examination revealed a well-developed and well-nourished young adult male who walked with great difficulty. At the level of the upper border of the third dorsal spinous process there was a midline sinus, about 1 mm. in diameter, with several hairs protruding from it, a typical pilonidal sinus. There was marked tenderness on pressure over the region of the second dorsal process, and just to the right of this a small deep-seated tumor mass could be felt. The remainder of the examination was negative but for the following neurologic findings. There was a paresis of the intercostal muscles on the left, below the level of the third interspace, as well as the left abdominal muscles. The abdominal reflexes were absent except for a weak response in the right upper quadrant. There was a spastic paraparesis of the legs, most marked on the left. The left foot was held in a equinovarus position. The knee and Achilles jerks were markedly hyperactive. There was an abortive ankle clonus bilaterally, most marked on the left. There were also bilateral

Babinski, Schaffer, Chaddock and Oppenheim signs. There was hypalgesia on the legs but no analgesia. Vibratory sense was lost in both ankles and absent in the left knee but present in the right. Position sense of the toes was lost on the left and impaired on the right. There was a positive Romberg sign. The gait was that of the spastic ataxic type.

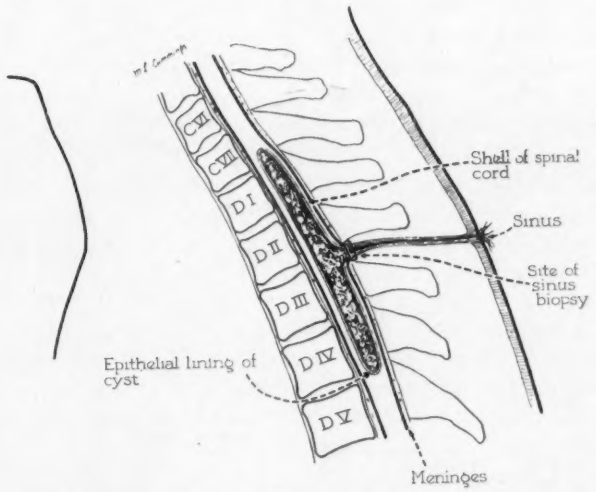

Fig. 3.—Midsagittal section showing diagrammatically the considerable vertical extent of the lesion. Note that the sinus passes between the spinous processes of the second and third dorsal vertebrae.

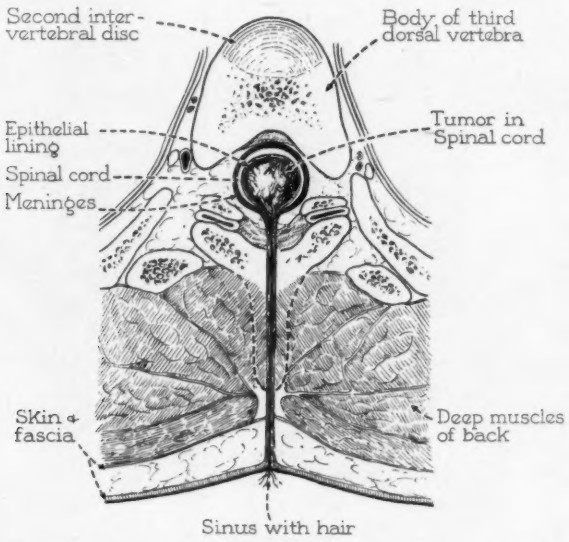

Fig. 4.—Cross section showing diagrammatically the lesion within the cord. Note that only a thin shell of spinal cord tissue is left about the tumor. The relation of the central canal of the cord to the lesion could not be determined.

Lumbar puncture done in the supine position showed an initial pressure of 165 mm. of water, but this dropped to 0 after the removal of 4 c.c. of fluid. The spinal fluid had an xanthochromic color and was clear. Testing for a spinal fluid block, one noted a good response on coughing, and a fair response on straining, while compression of the jugular veins produced a very slow rise of only a few millimeters with a similar fall.

Laboratory Studies.—The spinal fluid gave a positive carbolic acid and Nonne-Apelt reaction. Microscopic study revealed only red blood cells, probably due to

venepuncture. The Kahn test was negative; colloidal gold curve, 0221233210; mastic, 123321. The blood Kahn test was also negative, and routine blood and urine studies were essentially normal.

Roentgenograms of the spine revealed a widening of the spinal canal in the upper thoracic region, with an apparent thinning of the left pedicles of the first three or four vertebrae. There was a spina bifida occulta of the sacrum. A myelogram was undertaken, with 1 c.c. of iodized oil injected into the spinal canal in the lumbar region. The roentgenograms, shown in Fig. 2, with the patient in a 60° Trendelenburg position, revealed an abrupt stoppage of the oil at the level of the third dorsal vertebra. The upper margin of the oil column exhibited a concave pattern. These findings were considered to be diagnostic of a cord tumor.

Operation.—On May 11, 1936, under avertin anesthesia, Dr. Max M. Peet performed a cervical-dorsal laminectomy on the patient. An incision was made from the seventh cervical to the fourth dorsal vertebra. While stripping away the muscles, the dermal sinus was seen to extend down to the spine. The spinous processes and laminae of the last cervical and upper four dorsal vertebrae were removed, exposing the dura. This was covered by a very scant amount of epidural fat. The sinus was found to be connected to the meninges in the interspace between the second and third dorsal spinous processes. Upon opening the dura, and incising what appeared to be a thinned-out spinal cord, a large mass of sebaceous material containing a great number of hairs was encountered. This was removed by curettement. All of this material was intramedullary and only a shell of the spinal cord remained. Figs. 3 and 4 diagram these findings. The tumor was about 4 inches long, extending from the seventh cervical to the fourth dorsal vertebra. No attempt was made to close the dura, and the wound was closed without a drain.

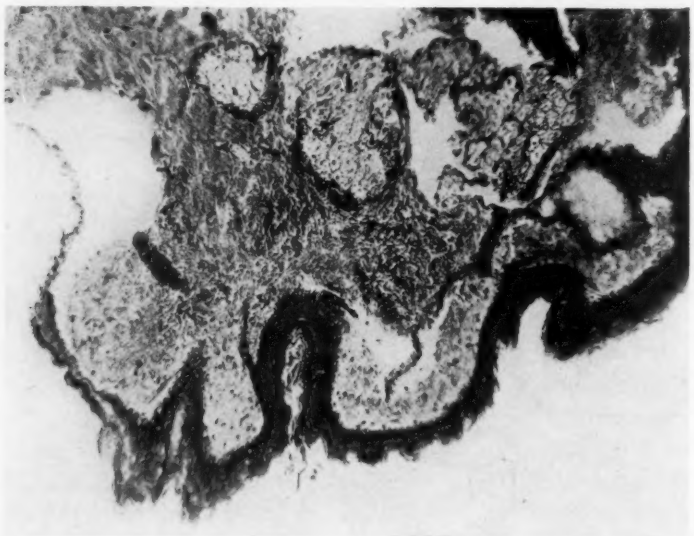

Fig. 5.—A high-power photomicrograph of curetted intramedullary tissue showing stratified squamous epithelium and sebaceous glands.

Pathologic Report.—Curettement of the cavity within the cord produced a fragment of tissue which was lined by a stratified squamous epithelium with associated hairs and sebaceous glands (Fig. 5). Microscopically the extradural sinus showed a tract of vascular pyogenic granulation tissue. In this there was a cordlike structure with a central lumen lined by stratified squamous epithelium and showing numerous hair shafts and sebaceous glands. This presented the picture of a pilonidal sinus. A cross section of this lesion taken just superficial to the cord showed

the sinus and granulation tissue surrounded with meningeal coverings and exhibiting numerous psammoma bodies (Figs. 6 and 7). Culture of the cyst contents was negative for growth.

Course in Hospital.—The patient's condition postoperatively was excellent after the first two days. He developed a mild urinary incontinence which required catheterization for ten days. His temperature returned to normal by the ninth postoperative day, at which time the skin sutures were removed. He was permitted up on the sixteenth day and was discharged about two weeks later.

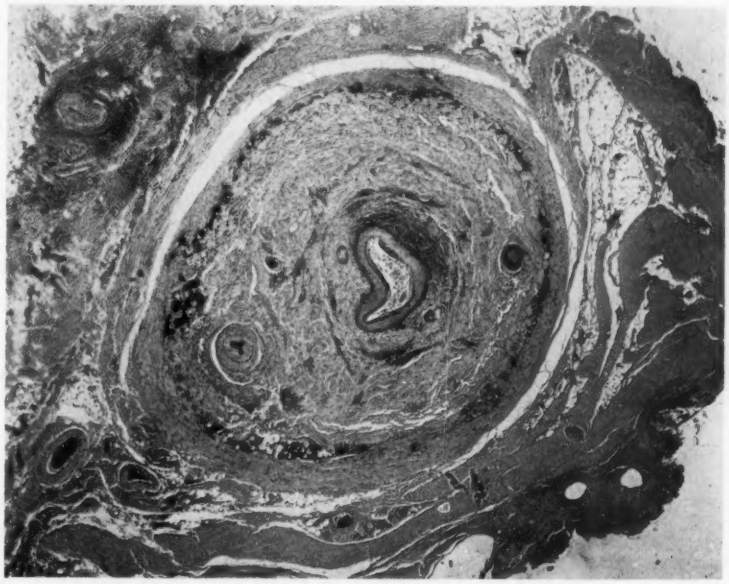

Fig. 6.—Photomicrograph of a cross section of the sinus tract leading from the skin to the spinal cord, with the section taken just proximal to the canal as shown in Fig. 3. The epithelial tract is surrounded by old granulation tissue. About the periphery the dura and arachnoid with psammoma bodies are seen.

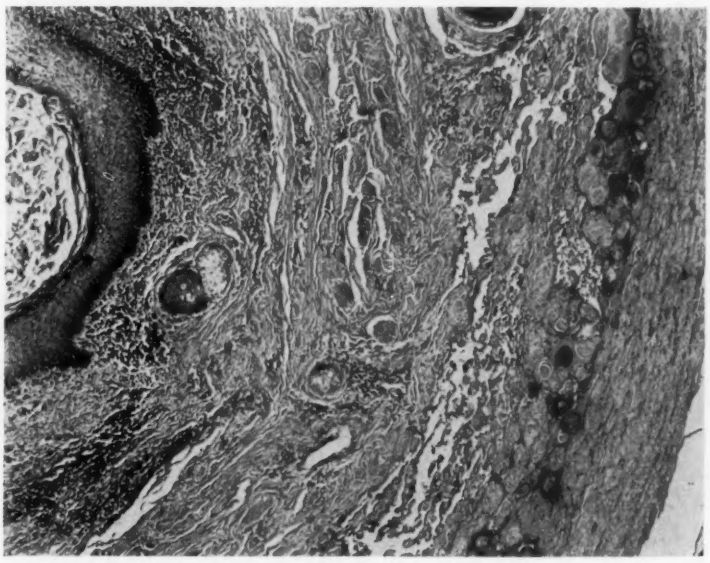

Fig. 7.—A high-power photomicrograph of the sinus tissue shown in Fig. 6. The central lumen, which is filled with hair and epithelial debris, is lined by a stratified squamous epithelium. To the right of the central lumen is a sebaceous gland. On the far right the line of psammoma bodies is apparent.

Subsequent examination four months postoperatively found him walking well, but complaining of an occasional mild pain in the left leg. One-half year later he registered no special complaints except of a mild weakness of the left leg and some tenderness in the scar. Examination four and one-half years postoperatively showed a mild residual paresis of the left leg and trunk, diminished deep sensation in the left leg, and a slight residual diminution of pain and temperature sensation below the fifth dorsal segment. However, the symptoms were minimal, and there was no evidence of recurrence. He has been able to complete his university training and is now actively engaged in his profession.

COMMENT

An analysis of this group of cases reveals the fact that pilonidal sinuses occurring over spinal segments higher than the sacrococcygeal region commonly communicate with the central nervous system. Of the 14 cases cited all but 1 were proved at operation. In 12 of these the lesion extended down to or within the meninges, while in the remaining case the lesion was intramedullary. The regional distribution of the sinuses was as follows: cervical, 1; thoracic, 5; lumbar, 3; and sacral, 5. In all but 2 cases there was an associated spina bifida. There was an even distribution as to sex. The ages ranged from 3½ months to 20 years, with only 5 of the patients over 5 years of age.

The signs and symptoms produced by these lesions were primarily neurologic. These were noted in infancy or early childhood in all but 2 of the proved cases, and ranged from a few days up to thirteen years in duration. As a rule the lesions occurring over the lower half of the spine became infected and produced either a subdural abscess or a meningitis. These cases manifested fever, rigidity of the neck and back, and all the other signs characteristic of meningeal irritation. The lesions occurring over the upper half of the spine usually showed no evidence of infection and presented the signs and symptoms typical of a cord tumor. Their common complaint was that of difficulty in walking, due to a spastic paralysis of the lower extremities. Sensory disturbances were usually mild or absent. The correct diagnosis, in the infected as well as the noninfected cases, was made possible only by the recognition of the midline sinus. Surgical removal of the lesion gave excellent results with only 1 mortality in 13 operated cases (7.7 per cent).

It is interesting to note that the patient whose case is herewith presented was apparently free of neurologic symptoms until he developed the measles, and that there was an exacerbation of the symptoms when he contracted chicken pox. These exanthems probably produced an inflammation of the sinus epithelium, increasing the pressure on the cord elements sufficiently to produce a paralysis. The recurrence of progressive symptoms at the time he entered college may be explained on the basis of sex changes incidental to puberty. Hormonal stimulation of hair growth and sebaceous gland activity might well result in an increased pressure within the lesion, sufficient to produce paralysis by pressure on the adjacent cord structures.

Origin.—It is generally agreed by research workers that pilonidal sinuses represent a congenital anomaly. However, there exist two main schools of thought as to the true origin of these lesions. The first school was originated by Herrmann and Tourneux[8] and Mallory,[10] and its views are currently being championed by Gage.[5, 6] This group maintains that these lesions are due to an abnormality in the development of the medullary canal, most commonly represented by a failure of obliteration of the same in this (sacrococcygeal) region. The second school, originated by Féré[3] and recently upheld by Fox,[4] maintains that pilonidal sinuses are due to either an infolding of the surface epithelium or a faulty coalescence of the same in early embryonic life.

The case herewith reported apparently presents new and additional evidence to the proponents of the first school. Obviously this case cannot be explained on the basis of a failure of obliteration of the medullary canal. However, the fact that this case, as well as most others reported occurring in the cervical, dorsal, and lumbar regions, showed a communication existing between the skin and the spinal cord or meninges suggests the probability of an incomplete separation of these structures in early embryonic life as the responsible factor. Normally the two medullary folds of the embryo fuse to form a medullary or neural tube, which after four weeks of intrauterine life has become completely separated from the overlying cutaneous covering from which it originated. In the present case the sinus probably communicated directly between the skin surface and the medullary canal which in the adult is represented by the central canal of the cord. This explanation seems all the more probable when the findings of Walker and Bucy's second case are considered. In their operative report, discussing work on an abscess lying in the meninges, they state: "The abscess was then opened up to a point where the cavity seemed to continue downward in a hole which appeared to sink into the dorsal surface of the spinal cord." It seems probable that this also communicated with the central canal of the cord.

This explanation for the origin of pilonidal sinuses is also tenable for the more common lesion occurring in the sacrococcygeal region. It must be borne in mind that the medullary canal was also present in this region during the early months of embryonic life, but that these tissues normally undergo atrophy and have usually become obliterated by the time of birth. Only by means of a microscopic study of serial sections of young embryos exhibiting pathology in the sacrococcygeal region can this theory be proved.

SUMMARY

1. A review of the literature reveals 13 cases of pilonidal sinuses occurring at spinal segments higher than the sacrococcygeal region. These cases are abstracted, and attention is called to the fact that the symp-

toms are primarily neurologic since these sinuses communicate between the skin and the central nervous system. Spread of infection from the sinus frequently produced signs and symptoms of either a meningitis or a subdural abscess. The noninfected group presented the clinical picture of a cord tumor.

2. A pilonidal sinus occurring over the third dorsal vertebra is described. This case differed from any heretofore recorded in the literature so far as its dilated cystic portion was found at operation to be intramedullary. The signs and symptoms produced by this lesion were typical of a spinal cord tumor.

3. The origin of pilonidal sinuses as a congenital anomaly is discussed. The case herewith reported suggests that these sinuses have their origin in a faulty separation of the medullary or neural canal from the overlying cutaneous epithelium.

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FUSOSPIROCHETAL ONYCHIA AND PARONYCHIA

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ONYCHIA and paronychia caused and sustained by fusospirochetal organisms are extremely rare judged by the scarcity of reports in the literature.

Heller[1] in his most comprehensive monograph on diseases of the nail quoted but two instances from the world literature up to 1927.

I have had the opportunity to observe one case of this condition of about two years' duration. The patient was almost uninterruptedly under medical care, but due to the peculiarity and rarity of the infection, neither were the causative organisms detected nor were efficient therapeutic measures carried out. These circumstances seem to justify the present report.

REVIEW OF LITERATURE

The oldest report found in the literature deals with observation of Carini[2] on onychia ulcerosa phagedenica. He observed in Brazil an epidemic of ulcerative processes, persistent and painful, localized on the toenails and ending in their destruction. The disease is known in Brazil under the name "*unheiro epidemico.*" The microbic flora of the ulcers consists in *Bacillus fusiformis* plus *Spirochaeta plaut-vincenti.* The victims of the infection are mainly peasants walking barefooted on the humid infested soil. Iodoform seemed to be effective against the fusospirochetal infection.

Aars Nicolaysen[3] observed two cases of fusospirochetal onychia. He also emphasizes the extreme rarity of this type of infection. He could not find any reference to this infection either in the great textbooks of surgery or in Klapp's monograph on panaritia. Prior to his observation, there were no publications on the subject in the whole Scandinavian medical literature.

His first case concerned a 62-year-old dentist with a swollen right index finger. The patient stated that a few days previously he had probably pricked his finger with an injection needle just used for the anesthesia at the extraction of a carious tooth. Within a few days the finger had grown worse and a wide incision made on the flexor side of the middle phalange showed the tissue to be grayish, discolored, and imbued with a thin, serous pus of a certain loathsome, foul smell. The tendon sheath seemed not to be affected, but the process was still progressing. Along the flexor and extensor side of the finger, incision showed the tissue comprising the flexor tendon and the basal phalangeal

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bone to be to a great extent necrotic. There were no signs of either lymphangitis or ascending tendovaginitis. Bacteriologic examination revealed fusospirochetal flora. Three injections of neosalvarsan (0.3, 0.45, 0.6 Gm.) brought about complete healing.

The second case related to a housewife, 54 years of age, whose right index finger had been severely bitten by her husband in an epileptic fit when she tried to keep his tongue clear of his teeth. The finger very soon started aching, growing steadily worse. The distal phalange of the right index finger was very tender and swollen, but in a rather diffuse manner without any firm infiltration or formation of abscess. From the two small wounds a blood-tinged serous fluid was discharged. The whole finger showed a diffuse edematous swelling, without any signs of either lymphangitis or tendovaginitis. Intravenous injections of neosalvarsan brought about healing.

Carone[4] reported the case of a 9-year-old girl who, about six months before she was seen, had had a splinter of wood under the fingernail of the right thumb removed by her mother by means of a nail. From that moment she suffered from a suppurative condition starting in the bed of the nail, spreading little by little to the distal phalange in spite of the surgical removal of the nail. The thumb, however, became swollen, the pain was violent, temperature went up to 38 to 39° C., and the distal phalange was exarticulated. This procedure, however, did not stop the progress of infection. The proximal phalange became swollen to twice its normal size and the skin around it was purple. Pressure elicited violent pain. X-ray showed the necrosis of the first phalange of the thumb. The first bacteriologic examination, six months after the condition started, of the fibrous exudate revealed a pure flora of fusospirochetal organisms.

Local application of arsphenamine did not change the clinical picture and in order to stop the progress metacarpophalangeal exarticulation was performed with multiple incisions in the surrounding soft tissues, which led to total cure.

Biopsy of different pieces of tissue removed at different points from the affected thumb showed a thick layer of necrotic and necrobiotic tissue, disintegrating cells embedded in a fibrin network, and a deep layer of tissue in the state of inflammation revealing a histiocytic reaction. There were no other characteristic signs.

CASE REPORT

A white boy, 17 years old, affected with hereditary dystrophy of the nails and hair,* came to the dispensary in March, 1938, suffering from onychia and paronychia of several fingers of about two years' duration. Since the start of the affection, he has always been under medical care; several times he has changed physicians and the curative measures applied have been changed without any success.

The hereditary dystrophy of the hair and nails was reported in J. Invest. Dermat. 4: 285-293, 1941.

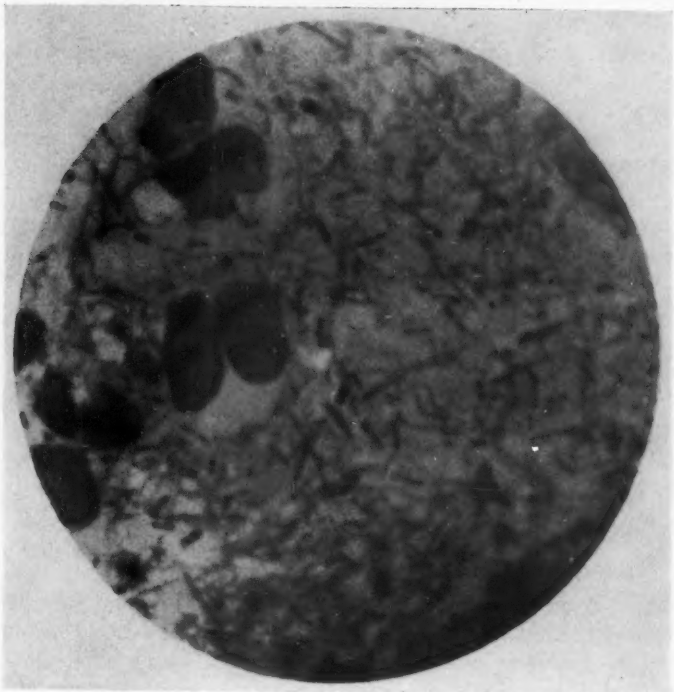

Fig. 1.—Smear from the thin fetid pus from underneath the affected nail. Gram stain. Photomicrograph, 1,500 diameters.

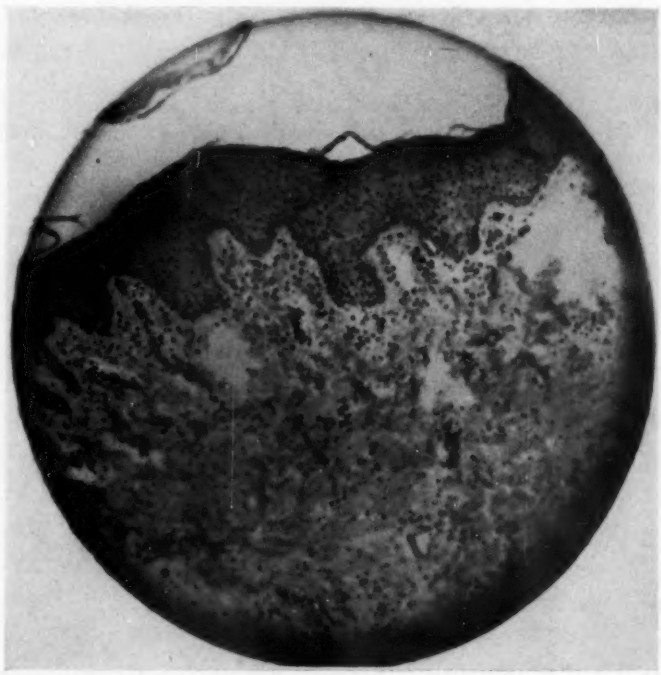

Fig. 2.—Section from the posterior nail wall of the right thumb. Hematoxylin-eosin stain. Photomicrograph, 500 diameters.

On admission the left hand showed onychia and paronychia on the third and fourth fingers, and on the right hand the first, third, and fourth fingers were affected.

The aspect of the affected fingers was the same. The nail wall was red, hot, swollen all around, and the redness was clearly marked toward the normal skin. The reddened area measured 5 mm. in breadth. The nail was loosened and stuck only under the posterior nail wall. The nail bed was deep red, covered with a thin grayish green, terrible fetid, pus of nauseating odor. The nail phalanges of the affected fingers were extremely tender.

The smell was so unbearable that he wore thick bandages on the affected fingers to lessen the odor, but these did only little good. If he took off the bandage, the smell in a few minutes was so bad in the consultation room that the window had to be opened.

Smears from the discharges of the affected nails showed pure culture of fusospirochetal organisms.

Further laboratory examinations showed: Wassermann and Kahn tests, negative; blood: hemoglobin, 70 per cent (Sahli); red cells, 4,100,000; white cells, 5,800; neutrophil polymorphonuclear leucocytes, 48 per cent; lymphocytes, 52 per cent; urine: normal, acid, specific weight 1.026; basal metabolic rate: satisfactory, variation plus 3.1 per cent.

X-ray revealed no changes in the distal phalanges of the affected fingers.

The nail wall of the right thumb was removed for histologic examination.

The section showed perfectly hyperkeratosis of the stratum corneum. Stratum granulosum was present throughout the whole section. The rete malpighii did not show acanthosis, but there was a moderate spongiosis throughout the whole section with the scattered infiltration of a few wandering cells. The lymph spaces and vessels, in the papillary portion of the corium, were somewhat dilated and surrounded with a moderate perivascular infiltration. The dilation of the vessels and lymph spaces of the deeper corium was more pronounced and there was also a somewhat denser perivascular infiltration consisting of small lymphocytes. Throughout the whole corium the connective tissue was edematous. No microorganisms of any description could be detected in the sections.

Concerning therapy, a 1 per cent aqueous solution of neoarsphenamine was tried as local application under the nail bed, without success. Afterward he was given three injections of neoarsphenamine, 0.3 Gm. intravenously every fourth day, without any result. Finally the nails of all the affected fingers were surgically removed and under antiseptic treatment cure was attained.

COMMENTS

The extreme rarity of fusospirochetal onychia and paronychia makes it understandable that nobody thought of this possibility in the course of this most annoying affliction of two years' duration.

Hudacsek[5] could not find among 6,000 cases of different, mostly severe panaritia during seven years a single case of fusospirochetal infection. Likewise, not a single case report could be found by painstaking search in the American literature. The present case thus seems to be the first report on fusospirochetal infection of the nail.

The total neglect of bacterioscopic examination of the peculiar thin fetid pus, of course, cannot be excused by the rarity of the condition.

Benedek, Zakon, and Harris[6] emphasized the absolute necessity of bacterioscopic examination in their observation of a likewise rare affliction of fusospirochetal osteomyelitis of the jaw. The present case is

again a warning not to neglect the bacterioscopic examination in every instance; in this case it would have saved two years' misery in the patient's life and spared the extreme annoyance for his family.

Among the few cases reported, Aars Nicolaysen's two observations have a special interest for us on account of the similar mechanism of the infection in my patient.

His first patient, a dentist, pricked his finger with an injection needle used in anesthesia of a carious tooth. His second patient was severely bitten by her husband in aiding him in an epileptic seizure.

In Carone's and Carini's cases injury was similarly an important element, but human saliva did not come in contact with the injured tissues at all.

From the description of his parents, my patient must have had a pompholyx of the nail bed anterior to the fusospirochetal infection of the nails. Moreover, he had the bad habit of gnawing on the dwarf nails.

In smears the oral cavity of this patient (tonsils, gums) revealed, at repeated instances, the presence of pure culture of fusospirochetal organisms, without the least sign of a fusospirochetal process on the oral mucosa.

With a high degree of probability it can be assumed that the patient having already a pathologic process in the nail bed (pompholyx) and having the habit of gnawing the nails, infected the nail bed with fusospirochetal organisms of his own oral cavity.

Fusospirochetal organisms do not start an infection primarily in healthy normal tissues. They easily invade, however, bruised, injured tissues causing and sustaining for a long time a more or less dangerous, slowly progressing infection.

At the first sight of my patient I had the impression that some extraordinary, unusual cause might play a decisive role in the onychia and paronychia. The long duration of the infection with surprisingly slow progress; the relatively moderate pain, at least in the beginning of the infection; the diffuse, edematous state of the nail phalanges without distinct localization of an evident center of suppuration; the total lack of lymphangitis and lymphadenitis; and last but not least, the thin grayish pus with the extreme fetid nauseating smell were the distinct features differentiating this type of infection from infections with common pus bacteria.

In Aars Nicolaysen's cases intravenous injections of arsphenamine had a prompt curative effect. In my case they totally failed.

In my judgment the best and most successful way of treating fusospirochetal infection (onychia, paronychia, osteomyelitis) is the surgical procedure of removing the anaerobic conditions (bruised, injured, or otherwise impaired tissues), the only adequate cultural conditions for the existence of these organisms.

SUMMARY

Onychia and paronychia caused and sustained by fusospirochetal organisms in a white boy, aged 17 years, are described, seemingly the first such observation in the American literature.

The condition lasted for two years with slow but definite progress, without lymphangitis or lymphadenitis.

Local application and intravenous administration of neoarsphenamine were without success.

Surgical removal of the nails of the affected fingers brought about prompt healing.

The necessity of prompt bacterioscopic examination of the discharge is urgently advocated in every case of this disease.

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MALIGNANT MENINGIOMAS

A Clinical and Pathologic Study

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DESPITE the voluminous literature concerning the meningeal tumors, little attention has been given to the malignant capacity which certain of these tumors exhibit, nor has there been any detailed consideration of those growths which microscopically have many of the characteristics common to the malignant tumors arising elsewhere in the body. Although a sarcomatous type of meningioma was included in the classification by Bailey and Bucy,[1] it has been infrequently reported and these authors stated that it is rarely encountered. Thus, Cushing and Eisenhardt[2] in their recent monograph found that but 6, or 1.9 per cent, of 313 meningeal tumors could be considered as malignant, and Baker[3] encountered 1 sarcomatous meningioma, or 1.1 per cent, in his series of 88 tumors. Globus,[4] however, expressed the opinion that sarcomatous meningiomas are not as rare as Bailey suggested and attributed the small percentage in published statistics to the fact that they are not fully recognized. Evidence to substantiate this can be found in the early report of Craig,[5] who encountered 11 examples, or 19.3 per cent, after a review of 57 cases at the Mayo Clinic. Penfield and his co-workers,[6] in a study of intracranial tumors and symptomatic epilepsy, noted the presence of 5 malignant meningeal tumors, sarcomas and fibrosarcomas, or 7 per cent, among 71 examples. Reports of large series of intracranial meningeal tumors are not frequently published, but from those available it can be noted that the percentage of malignant meningeal tumors varies considerably. In several of the reports, such as that of Frazier and Alpers,[7] no mention of the malignant variety is made.

In the present study, 370 intracranial meningeal tumors seen at the Mayo Clinic were examined microscopically. Of this group, 36 were selected on the basis of the microscopic examination as showing definite malignant characteristics. With but few exceptions the 370 tumors were operative specimens and in some cases both surgical and necropsy material was available for study. Certain limitations were made concerning those malignant tumors selected for study in that only those were chosen which were formed growths and which could be classed under the broad heading of meningioma as it conforms to the conception

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among neurosurgeons and neuropathologists. Thus, 5 cases of perithelial sarcoma of the cerebellum, such as were described by Bailey,[8] were not included. A single example of a highly malignant cerebellar sarcoma of the Ewing type, probably vascular in origin, as well as a case of oat-cell neoplasm, was also excluded. The latter was possibly metastatic from the lung although this was not evident clinically. One very unusual osteogenic sarcoma of meningeal origin encountered in the series has been the subject of a separate report.[9]

Of the 36 growths selected for study, 22 occurred in men and 14 in women. As is to be expected, the majority, 22 in number, occurred in the third, fourth, and fifth decades with the extremes at the ages of 8 and 60 years.

CLASSIFICATION

Because of the variable degree of malignancy exhibited in the microscopic appearance of the different tumors and the different morphologic characteristics, it is necessary to attempt some grouping as a basis for study and classification. The classification was derived essentially from the microscopic appearance of the tumors studied, and although the basic feature was the grading of the degree of malignancy, some attempt was made also to identify the major structural elements of the tumors. It is recognized that any such classification, in a large sense, must be arbitrary and that no sharp line of demarcation exists between the different components.

In meningeal tumors of early or low-grade malignancy, the malignancy, in general, is reflected in the tissue architecture rather than in the cell type. These tumors are highly cellular and vascular, usually with little variation in cell and nuclear size and structure. Little evidence of psammoma formation is present. Whorls, if present at all, are not prominent, and usually a definite pattern to the tissue is lacking. Mitotic figures are present in moderate numbers. Giant cells, if present, are in early forms.

In meningeal tumors with advanced or well-marked malignancy, the malignant character of the tumor is reflected in the cell type and structure as well as in the general tissue architecture.

A. Tumors of meningothelial or related type with malignancy evident in the parenchyma, as contrasted with the following subgroup, are cellular tumors with little or no whorl or psammoma formation. Mitotic figures are abundant and giant cells are frequently encountered in many of the tumors. There is considerable variation in size and type of cells. The tumor is quite vascular. The stroma is well demarcated from the parenchyma and may be scanty. There may be invasion of dura, brain, bone and often of the stroma of the tumor itself. Many of these growths are composed of large epithelioid cells.

B. In the sarcoma-like form, manifest in the fibroblastic variety of tumor or derived from the stromal elements of other forms, there may

be the characteristic streaming, interlacing pattern of a fibroblastic tumor, or the pattern of the tissue may be quite irregular and broken. In the latter instance, giant cells and bizarre forms may be encountered. Mitotic figures are present, usually in large numbers.

Malignant tumors of variable activity, possibly arising from the dura itself, are related to the foregoing group but take on certain of the characteristics of other forms; that is, the fibromyxosarcoma, fibrochondrosarcoma or osteogenic meningeal sarcoma. These are highly malignant, atypical growths which have an unusual and bizarre microscopic appearance with numerous giant cell forms and other atypical cells, and probably are atypical stromal tumors related to the sarcomatous form.

As can be seen, no attempt has been made to include in the classification the perithelial tumors (peritheliomas and perithelial sarcomas) described by Bailey and by Hsü,[10] the diffuse or formed melanoepitheliomas,[11, 12] or the reticulum-cell sarcoma described by Yuile[13] which is probably related to the perithelial sarcoma if not identical with it. The so-called primary fibroblastoma of the brain, examples of which have been described by Mallory[14] and by Cottrell,[15] is considered to fall in the group of sarcomatous meningeal tumors. The apparently intracerebral situation of some of these can be explained upon a leptomeningeal origin deep within a sulcus. No mention has been made of the clinical aspect of the various groups; this will be considered along with the individual tumor types.

MENINGEAL TUMORS OF LOW-GRADE MALIGNANCY

The consideration of these tumors of low-grade malignancy but, nevertheless, of vigorous growth is a necessary preliminary to the consideration of those which exhibit advanced malignant characteristics. As has been stated, it is this group of meningeal tumors that has received the least attention, for whatever consideration has been given to the malignant meningeal tumors has been directed to those which are obviously sarcomatous and, in most instances, highly malignant. Twenty-two tumors were studied in this group and among these were all the variations of structure encountered in the meningeal tumors. Although within the group there were variations in the degree of activity, the grading of these meningeal tumors cannot be carried too far. Certain common characteristics of cell structure and tissue architecture were present and will be considered.

The 22 tumors were equally distributed between male and female patients with age extremes of 12 and 57 years. All but 2 of the tumors occurred in the third to the fifth decades. More than one-half of the tumors were removed from the frontal or frontoparietal region, and others were distributed over the remainder of the brain. One growth occurred in the cerebellopontine angle and one, apparently originating in the torcular region, involved both sides of the tentorium. Of the size and extent of the tumors, more information will be given later.

There was considerable variation in the duration of symptoms as figured to the time of the first admission to the hospital. In 12 of the 22 cases, symptoms of one sort or another had been present for one year or less. The longest history was six years in the case of tumor of the sphenoid ridge in a 47-year-old woman. At operation this tumor was found to have extended widely throughout the anterior cranial fossa, and despite a grossly complete removal, the patient died seven months after operation with symptoms suggestive of recurrence of the tumor. In one instance there was a five-year history and at operation a subtotal removal of a tumor of the tuberculum sellae was carried out. Death followed from postoperative complications and at necropsy the tumor was found to have extended superiorly sufficiently to compress the left lateral ventricle and third ventricle and to have invaded the sella turcica. In 7 of the 22 cases there were histories varying from three to six years in duration and for these 7 the average duration of symptoms was just more than four years. In the remaining 15 cases, the duration of symptoms was two years or less and the average for these was between eleven months and one year. The average duration of symptoms for the entire group was two years and three months.

The duration of symptoms alone is a poor index of the rapidity of growth of a tumor, and it is obvious that tumors situated over relatively silent portions of the hemisphere will attain large size and even extend widely before making known their presence. As an example, one patient having a three-year history was found to have a large frontoparietal tumor which had penetrated the calvarium and extended widely beneath the scalp. Similarly, one growth originating apparently from the torcular region was found to measure 10 cm. in width at the time of operation and had caused erosion and multiple regions of destruction in the occipital bone. It had invaded the tentorium and presented on either side of it. One meningeal tumor was found in the cerebellopontine angle in a patient having a history of two years' duration. At operation it was found to have invaded and penetrated the tentorium, causing compression of the supratentorial structures as well as extending between the pons and the cerebellum and between the cranial nerves.

Involvement of the bone was present in 8 instances. In 2 cases definite invasion and penetration had occurred and erosion and destruction of bone were noted in the torcular tumor described previously. In 4 instances, in all of which there were histories of ten months' duration or less, hyperostosis with increased vascularity was evident.

In this group evidence of recurrence of the tumor occurred in 8 instances in which there was an average duration of seven and one-half months between the time of operation and the first symptom. In one instance in which symptoms had been present for nine months prior to operation, a second operation five months later disclosed a recurrent tumor as large as that removed at the first operation. One month later

all the former signs of recurrence of the tumor were again present. The necessity of care in the interpretation of figures for recurrence may be shown by the case of a 12-year-old girl who had evidence of an intracranial tumor for six months prior to the removal of a large intracerebral growth. Despite undoubted clinical evidence of recurrence five months after operation, death did not occur until two and one-half years later.

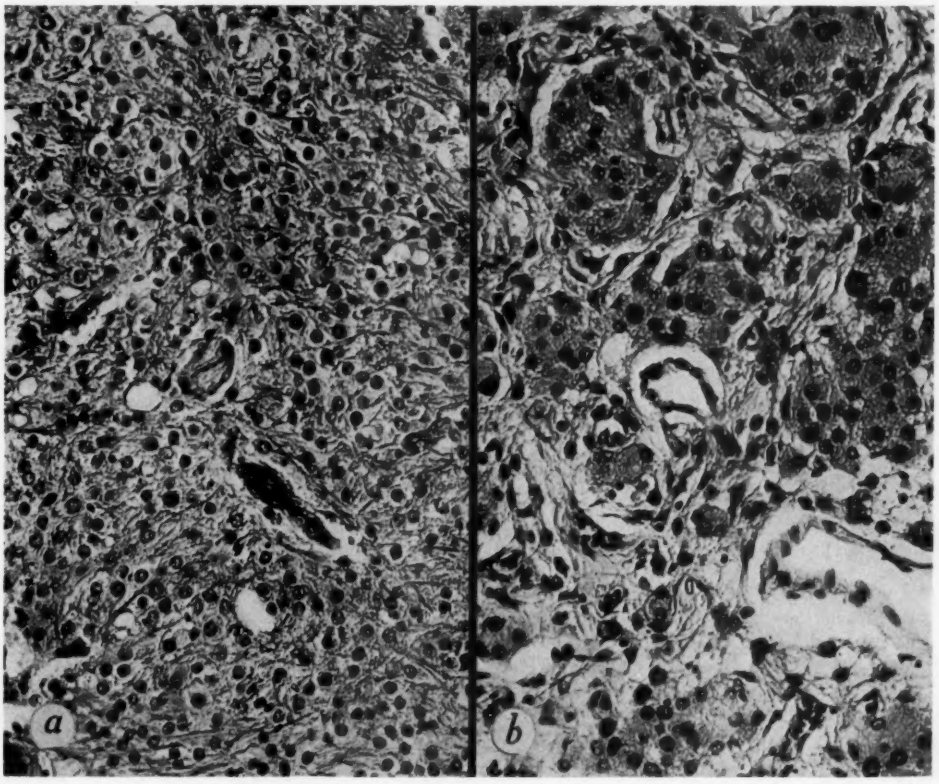

Fig. 1.—Tumors of low-grade or early malignancy. *a*, Note the epithelioid type of cell with well-defined cytoplasmic outlines, the cellularity of the tissue, and the absence of variation in cell size (hematoxylin and eosin ×200). *b*, Note the chromophilic nuclei and moderate variation in the size of the cells. This tumor contained many giant cells and mitotic figures (hematoxylin and eosin ×220).

Pathology.—No attempt will be made to divide the tumors of this group further upon the basis of differences in tumor activity. However, for the purposes of description several morphologic groups have been separated. Certain characteristics are common to all these meningeal tumors of low-grade malignancy and will be considered first. A characteristic feature of almost every tumor in this group was the marked cellularity of the tissue (Fig. 1*a*). Associated was a high degree of vascularity, almost all of the vessels being well formed but thin and related to the stromal elements. The latter varied in different tumors and in some showed unusual overgrowth such as is often seen in certain of the gliomas. The number of mitotic figures seen in the different

tumors varied but in none were they abundant. The architecture varied somewhat with the morphologic character of the tissue. In the fibroblastic tumors considerable streaming and some tendency toward whorl formation about the vessels were seen, but discrete whorls and psammoma formation were present to any marked degree in only one growth. Lobulation of the tissue was present in several of the growths, particularly when the connective tissue was prominent and the tumor was of the meningothelial variety. Giant cells, as such, were rarely seen, although in several of the tumors early forms were evident. The cell structure varied with the tumor type, but in general there was little variation in the size of the cells or of the nuclei. Calcification was rarely seen and, when present consisted of a few scattered deposits.

In this group there were four tumors in which the parenchyma was composed of columns and cords of large epithelioid cells. These corresponded closely to the Type V of Cushing and Eisenhardt, three being similar to their Variant 1 and one to their Variant 2. The individual cells were large and cuboidal or polygonal with abundant finely granular cytoplasm and large chromophilic nuclei (Fig. 1*b*). In several of the growths there were scattered regions in which the cells appeared round or fusiform. In one tumor there was considerable variation in the size of both nuclei and cells, and large and often atypical nuclear forms were encountered frequently. All the tumors were well vascularized and contained a moderate amount of connective tissue distributed in strands between the cell groups. No reticulum or collagen formation was noted. There was no marked perivascular arrangement, and only in one of the growths was there a suggestion of whorl formation. All the tumors contained a moderate number of mitotic figures.

The malignant appearance of these tumors has been commented upon by Cushing and Eisenhardt, who stated that sarcomatous-like regions were encountered in several of their 18 examples. In general, these four growths represent the most active of the group of low-grade malignant meningiomas. Peculiarly enough, the duration of symptoms prior to operation in the 4 cases ranged from six months to six years.

In the group of low-grade malignant meningiomas, the differentiation between those of parenchymatous and those of stromal origin is frequently difficult and often the morphologic character of the tumor is not clear. In the group there were 4 tumors considered to be of connective tissue origin. In only 1 was the fibroblastic character highly developed (Fig. 2), and in this tumor early giant cell forms could be identified. All the tumors showed some tendency toward streaming, but with the exception of that noted previously, this was not marked. Mitotic figures were not abundant and several tumors appeared to consist of a mixture of meningothelial and fibroblastic elements.

There were marked differences in the tissue architecture and cell type in the remaining 14 tumors. In general, all appeared to be related to

the meningothelial variety and all were quite cellular and highly vascularized. An occasional one appeared to be almost hemangiomatous owing to the frequency with which small but well-formed vessels were encountered. Whorl formation was not marked in any, but in several the tissue showed well-formed lobules due to the manner in which the stroma was disposed. Mitotic figures were present in all the group, but in none were they abundant. Giant cell forms were not seen.

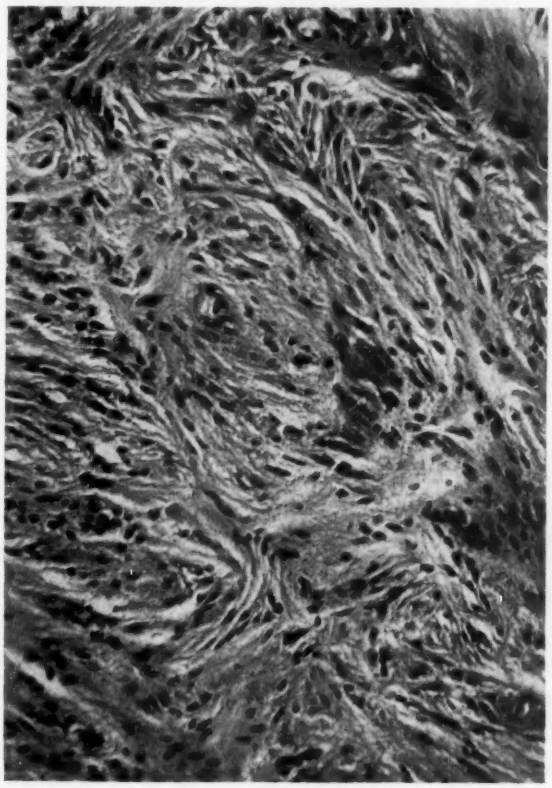

Fig. 2.—Highly cellular tumor of low-grade malignancy and of stromal origin (hematoxylin and eosin ×180.)

MENINGEAL TUMORS OF PRONOUNCED MALIGNANCY

In this second group of meningeal tumors in which the malignant character was more pronounced, the change was evident microscopically both in the cell structure and in the architectural arrangement of the tumor tissue. There were 14 tumors in this group and they will be considered together for clinical purposes.

Of the 14 tumors, 11 were in male patients. The age distribution was not unusual with the exception of an 8-year-old child from whom a large frontoparietal growth was removed. It is of interest that in this same family another child had died at the age of 5 years with the symptoms of stiffness of the legs, tremor, and headache, a diagnosis of gumma cerebri having been made by the family physician.

The duration of symptoms for this group was considerably lower than for the group previously considered. In one instance the data relative to the occurrence of the first symptoms were lacking, although this patient underwent, at various hospitals, five operations for recurrence of a parietooccipital tumor. The interval between the first and the second operation was three years and six months, and the interval between the third and the fourth operation was seven months. Of the 13 remaining cases, the average duration of symptoms prior to operation was eighteen months. This includes 4 cases in which the interval between the first symptoms and operation varied from two to five years. In 2 of these 4 cases the tumor was frontal and in 2 it was frontoparietal. Excluding the aforesaid cases, the average duration of symptoms was six months. In 6 of the cases, the duration of symptoms was less than one year.

In 5 instances there were changes in the adjacent bony structures. Primary invasion and perforation of the skull occurred twice, once in a flat tumor in which both an intracranial and an extracranial mass were present, and once in a parasagittal frontal growth which had invaded the frontal and ethmoid sinuses and had caused considerable destruction of the adjacent calvarium. In 2 instances, in both of which the tumor was frontal, erosion of the bone was observed on roentgenographic examination. One growth had caused hyperostosis of the inner table of the frontal bone, and seven years after operation recurrent tumor was present both in the calvarium and beneath the scalp. In the case noted previously with multiple recurrences, invasion of the calvarium and of the mastoid bone was present at the last operation.

Pathology.—Of the 14 tumors, 8 were in the frontal or frontoparietal region. Grossly, they varied from moderately well circumscribed global masses to the flat, *en plaque* variety. On the basis of the microscopic appearance the tumors of this group have been separated into two subdivisions. The first group consists of those tumors which, although obviously malignant, have retained certain of the characteristics of the meningothelial tumors; in these the malignancy can be said to be of "parenchymatous" origin. In the second subdivision the tumors can be considered to be sarcoma-like and the tumor tissue of stromal origin. These subdivisions will be considered separately.

There were 6 tumors in the former group. In all of these the tissue appeared to be more or less epithelioid, related to those described by Cushing and Eisenhardt as nonreticulin or collagen-forming epithelioid tumors (Type V). They appeared to have, however, more of the malignant characteristics than the similar growths described in the previous group. The essential microscopic appearance of each of the 6 tumors will be given.

CASE 1.—A large frontal parasagittal tumor was removed from a 38-year-old man. Roentgenographically, there were regions of destruction in the overlying calvarium. Microscopically, the tumor showed definite invasion of the dura mater

and the brain. The tumor was composed of sheets of large cells with hyperchromatic nuclei of varying size. In some regions the tissue appeared epithelioid and elsewhere meningotheliomatous. Giant cells were plentiful and mitotic figures moderate in number. The tissue architecture was irregular with no whorls. The tumor was highly vascular, but there were extensive regions of degeneration.

CASE 2.—A large, frontal, parasagittal tumor occurred in a 57-year-old man who had a three-year history complicated by several episodes of local trauma. Microscopically, the tumor appeared well encapsulated and composed of cords and columns of polygonal cells, similar in many respects to those of the epithelioid variety (Fig. 3*a*). The nuclei were hyperchromatic and showed considerable variation in size and shape, and occasional giant cells were observed. There were a moderate number of mitotic figures. The cell columns were separated by vascularized strands of connective tissue which were invaded by the tumor parenchyma (Fig. 3*b*).

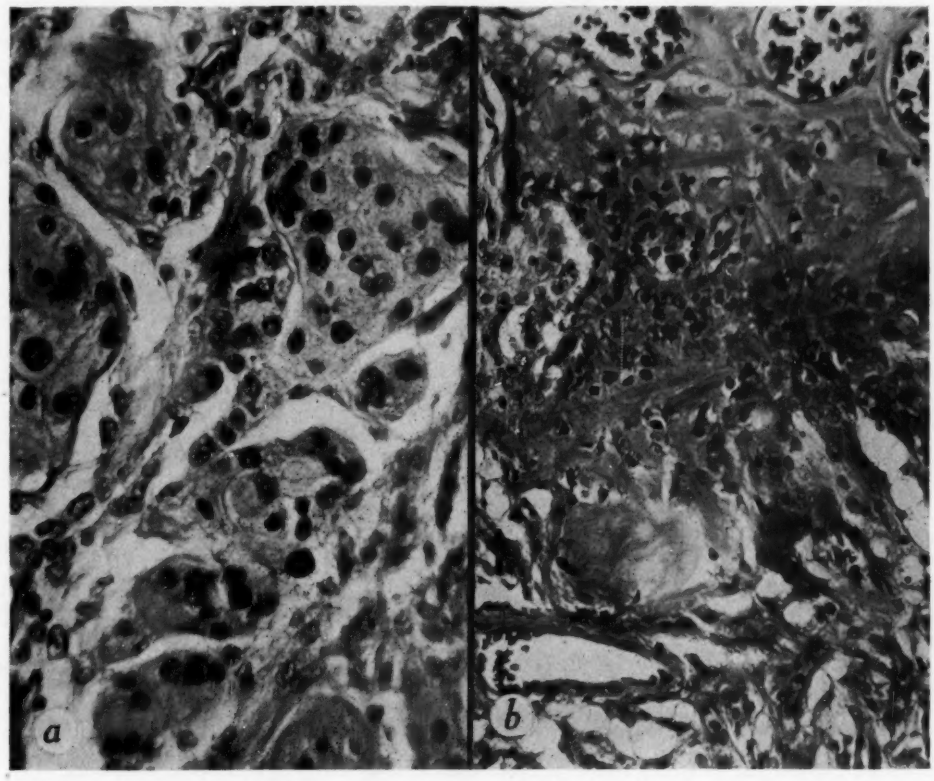

Fig. 3.—Case 2. Highly malignant tumor of parenchymatous origin. *a*, High magnification to show the character of the individual cells. Note the marked variation in the size of the nuclei and the mitotic figures. Tumor of epithelioid type (hematoxylin and eosin ×300). *b*, To show invasion of the supporting stroma by tumor cells. There has been invasion of a band of hyalinized connective tissue about several vessels (hematoxylin and eosin ×205.)

CASE 3.—A large occipitoparietal growth was removed from a 36-year-old man who had had symptoms for nine months prior to operation. Objective signs of recurrence were present seven years after operation, and at the time of the second operation, five years later, the tumor had invaded and perforated the calvarium and there was involvement of the falx, the longitudinal sinus, and the tentorium. Microscopically, the tumor was composed of nests, small whorls, and columns of cells separated by edema and hyalinized connective tissue (Fig. 4*a*). The tissue architecture was quite disorganized. The tumor cells varied in type and size. Some

were elongated, and others appeared polygonal. Bizarre, atypical, multinucleated, giant cells were abundant and mitotic figures were frequently encountered. The tumor was vascular.

CASE 4.—An extremely large tumor arose from the sphenoid ridge in a 60-year-old woman with symptoms for one year prior to operation. Microscopically, the tumor was very cellular and was composed of small groups and sheets of very large, epithelioid cells (Fig. 4*b*). There was an occasional suggestion of whorl formation. Reticulin was not present and there was no evidence of collagen formation. The cells contained an abundance of finely granular cytoplasm and large, hyperchromatic, and often pyknotic nuclei. There were no psammoma bodies and only scattered mitotic figures. The tumor was atypical and represented a less malignant form than those already described. Only an occasional giant cell form was seen.

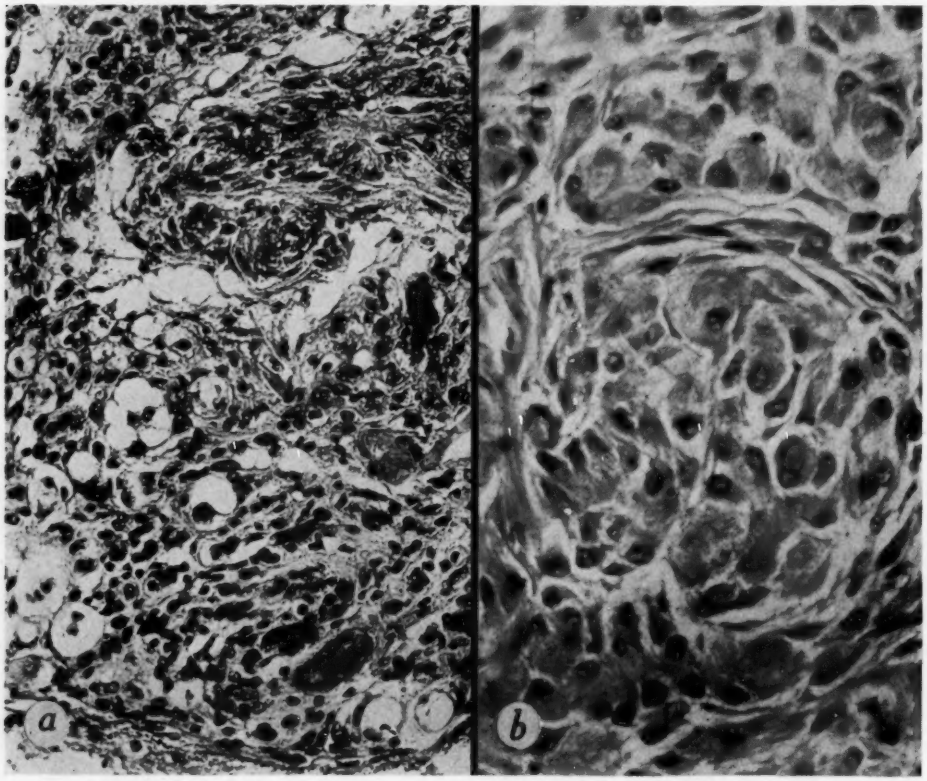

Fig. 4.—Malignant tumors of the parenchymatous type. *a*.—Case 3. To show the marked vascularity of the tumor tissue and the presence of giant cells with atypical nuclei (hematoxylin and eosin ×220). *b*.—Case 4. Atypical epithelioid tumor showing variation in the size of the large cells which contain an abundance of finely granular cytoplasm (hematoxylin and eosin ×330).

CASE 5.—A tumor was removed from the right occipital region of a 37-year-old man who had had symptoms for sixteen months prior to operation. Recurrence of the growth was evident three years following operation. Microscopically, the tumor was composed of columns and cords of typically epithelioid cells which showed extreme variation in size and shape. Mitotic figures were abundant and there were many atypical giant cell forms (Fig. 5*a*). Marked invasion of the brain and even of the intrinsic stroma of the tumor was present (Fig. 5*b*). Some tendency toward a perivascular arrangement of the tumor cells was seen in some portions of the growth. The microscopic appearance was of a highly malignant tumor.

CASE 6.—A large parasagittal tumor was situated above the crista galli in a 55-year-old man who had had symptoms for two years prior to operation. At operation the tumor was found to have invaded the frontal and ethmoid sinuses as well as the falx and the longitudinal sinus. Microscopically, the tumor appeared to be intermediate between meningioma and glioma. The cells contained discrete, deeply staining nuclei which varied in size but which were moderately large. There was also considerable variation in cell structure. Some cells appeared polygonal and epithelioid, but elsewhere they were not unlike those of the glioma series. Special stains did not disclose evidence of glial fibers, although the cells were well stained by phosphotungstic acid-hematoxylin. There was some tendency toward perivascular arrangement in some regions where the cells appeared more active. Mitotic figures were moderately abundant and there were occasional forms suggestive of giant cells. The tumor contained little stroma and there was definite invasion of the adjacent brain tissue.

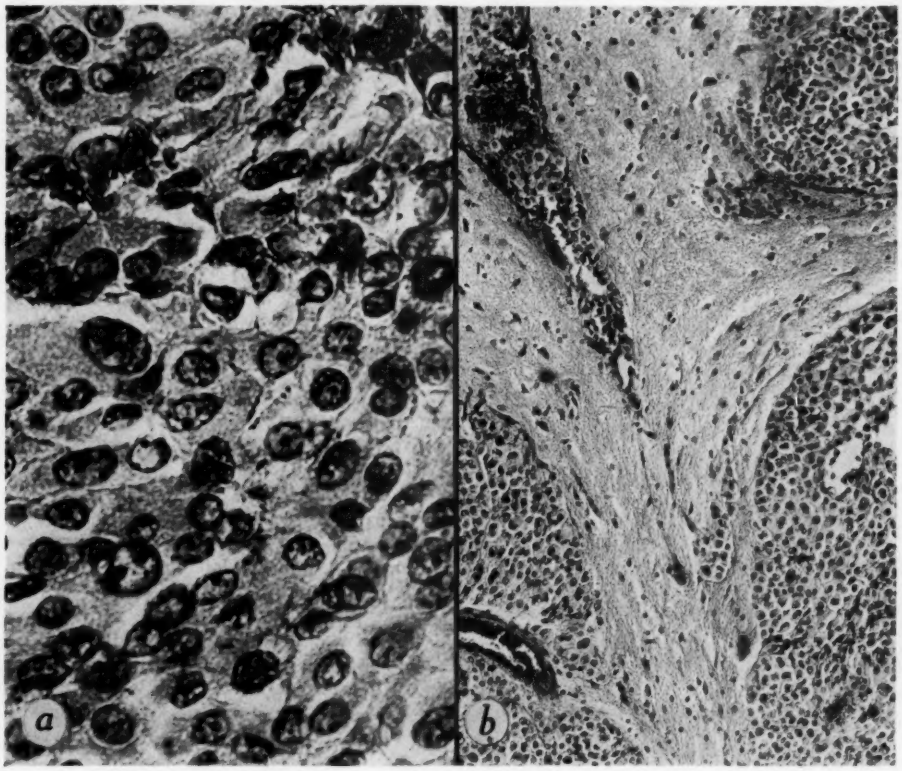

Fig. 5.—Case 5. Malignant tumor of parenchymatous type, epithelioid variety. *a*, High magnification to show the character of the cells. Note the variation in size of both the cells and the nuclei and the numerous mitotic figures in different stages of progression (hematoxylin and eosin ×470). *b*, To illustrate invasion of the brain by tumor. The brain tissue seen in the photograph was completely surrounded by tumor and well within the limits of the growth (hematoxylin and eosin ×85).

There were five highly malignant tumors which were undoubtedly of a sarcomatous type and one growth of a lesser grade of malignancy which appeared to be a fibromyxosarcoma. There was considerable difference in the architecture of these growths and three structural types could be separated. One type appeared to resemble typical fibrosarcoma with streaming cell bundles and a definite tendency toward an interlacing

pattern. A second type, apparently closely related to this, was a highly cellular hemangiosarcoma with no definite pattern to the tissue. This type, of which there was one example, appeared to be intermediate between the first type and the Ewing type of growth. The third type was the very active, somewhat atypical tumor of connective tissue origin in which the tissue pattern appeared disorganized and irregular, and which contained many giant cells and abundant mitotic figures. Because of the unusual character of these tumors they will be described individually.

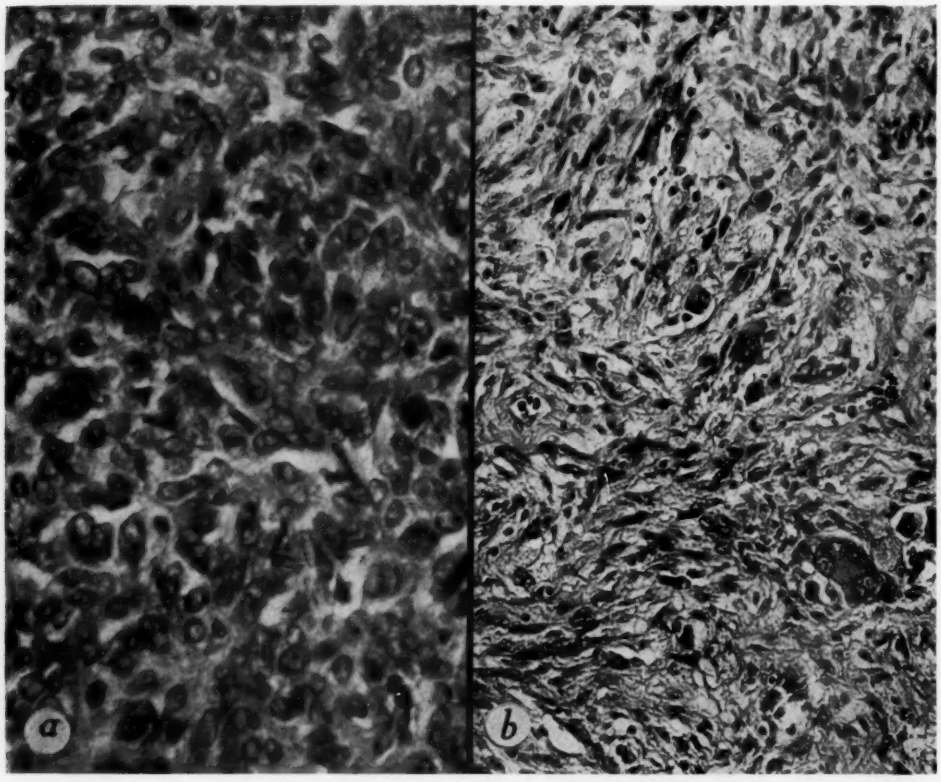

Fig. 6.—*a*, Case 8. Highly malignant hemangiosarcoma for comparison with other malignant tumors of stromal origin. Note the cellularity of the tissue and the presence of numerous mitotic figures (hematoxylin and eosin ×450). *b*, Case 9. Rapidly growing malignant tumor of stromal origin. Note the presence of giant cells, mitotic figures and irregular tissue pattern (hematoxylin and eosin ×220).

CASE 7.—A specimen from a recurrent parieto-occipital tumor was removed from a 47-year-old man. This growth has been previously referred to in regard to the numerous and rapid recurrences after removal. Microscopically, the tumor appeared to be a rapidly growing, highly cellular fibrosarcoma. The cells varied in size and shape from those typically fibroblastic to those which appeared but slightly elongated or oval. The nuclei were prominent and chromophilic and there was a moderate number of mitotic figures. In some areas, where the cells appeared elongated, streaming and interlacing of cell bundles occurred, but elsewhere the cells were disposed in sheets. No giant cells were observed. A rather heavy capsule to the tumor showed marked invasion by tumor cells.

CASE 8.—An extensive tumor arose from the inferior border of the falx at the angle between the falx and the tentorium. The patient was a 32-year-old man and symptoms had been present for six weeks prior to operation. Microscopically, the tumor appeared as a highly cellular growth in which the cells were closely approximated with no characteristic pattern (Fig. 6*a*). The cells appeared slightly elongated and contained deeply staining nuclei which showed little variation in size or shape. Only occasional giant cells were observed. There was little stroma aside from the presence of a fine intercellular reticulum. There was little degeneration despite only a moderate number of vessels which were rather widely spaced. Mitotic figures were abundant. A section of dura attached to the tumor showed marked invasion. This tumor appeared to be one of the malignant hemangioblastoma group and might be classified as a hemangiosarcoma. It is included in the group of malignant meningiomas for purposes of comparison and to illustrate the occurrence of tumors of vascular origin in the supratentorial region.

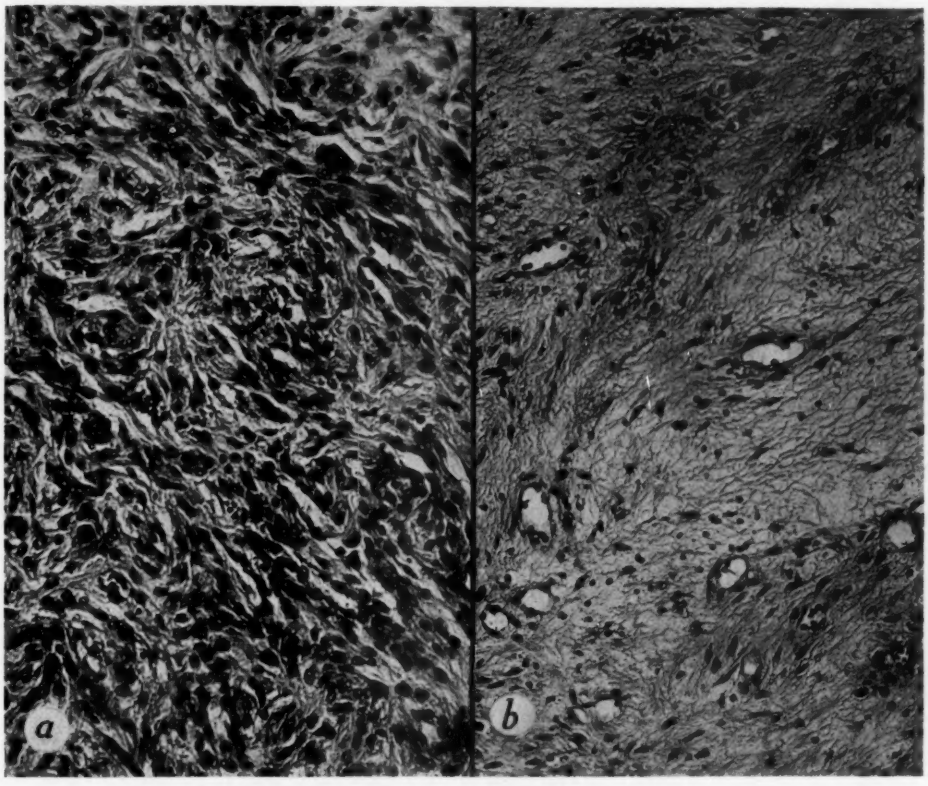

Fig. 7.—*a*, Case 10. Malignant tumor of stromal origin. Note the cellularity of the tissue and the hyperchromatic nuclei. Several giant cells are present (hematoxylin and eosin ×220). *b*, Case 12. Fibromyxosarcoma. Note the cellular areas separated by myxogenous tissue and the numerous small vessels (hematoxylin and eosin ×160).

CASE 9.—A parasagittal tumor measuring 8 by 6 cm. was removed from the frontoparietal region of an 8-year-old boy in whom symptoms had been present for six months prior to operation. Microscopically, the tissue was composed of large cells showing considerable variation in size and an abundance of large, atypical multinucleated giant cells (Fig. 6*b*). The tissue pattern appeared considerably disorganized, although characteristic streaming was evident throughout. The cell nuclei appeared large, irregular, and hyperchromatic, and mitotic figures

were abundant. The growth is regarded as a highly anaplastic form of malignant meningioma of connective tissue origin.

CASE 10.—A large tumor 8 by 6 cm. in diameter arose in the frontoparietal region of a 40-year-old woman. Symptoms had been present for five years prior to operation. Microscopically, the tissue had an irregular pattern but with some interlacing and streaming of cell bundles (Fig. 7*a*). The individual cells appeared large and elongated and contained deeply staining nuclei. There was considerable variation in cell size and numerous large multinucleated cells were present. A moderate number of mitotic figures were present. The tissue was cellular and contained many small vessels.

CASE 11.—A growth measuring 10 cm. in diameter was removed from the right prefrontal region of a 37-year-old man who had had symptoms for about two months prior to operation. Recurrence of the tumor was evident about one year after operation. Microscopically, there appeared to be somewhat less streaming than in the other growths. In some regions there was an occasional whorl about vessels. Mitotic figures were present in moderate numbers, as were giant cells. Nuclei appeared large and hyperchromatic. The tissue was quite cellular and highly vascular.

CASE 12.—As has been noted, one growth was classified as a fibromyxosarcoma. This was an hourglass type of tumor removed from the parietal region of a 44-year-old man. He gave a history of having had a small mass, not unlike a sebaceous cyst, over the parietal region for about six weeks prior to admission. At operation this was found to be the extracranial portion of a flattened tumor which had perforated and invaded the skull. The intracranial portion, which apparently had taken origin from the region of the longitudinal sinus, had invaded the dura.

Microscopically, the growth was poorly encapsulated. The tissue was composed of typical elongated fibroblastic cells in large and small groups separated by wide regions of highly myxomatous tissue (Fig. 7*b*). Mitotic figures were moderately numerous, particularly in the more cellular regions where the tissue had no characteristic pattern for the most part. However, in some portions there was a moderate amount of parallelism and streaming of cell bundles. The growth was extremely vascular, with thin-walled vessels which in some places had the appearance of being formed by the neoplastic cells themselves. In general, the tissue had a loosely woven appearance and this was true even of the more cellular portions.

ATYPICAL TUMORS OF UNCERTAIN ORIGIN

There were two growths which, although of undoubtedly meningeal origin, were highly atypical and which because of their unusual character were not placed in either of the preceding two groups. Although both of these tumors were probably of stromal origin, they showed sufficient variation from those previously described to allow being considered separately.

CASE 13.—A left basofrontal tumor measuring 6 cm. in diameter was removed from a 49-year-old man who had had symptoms for seven months prior to the first operation. Evidence of recurrence of the growth was present eight and one-half months after operation despite radiation in the interval. At the second operation, eleven months after the first, the tumor was found to have extended bilaterally. Microscopically, the tissue appeared quite atypical and varied considerably in different portions of the tumor. For the most part, the individual cells were elongated and spindle-shaped, containing rather large, chromophilic nuclei which varied moderately in size. In some regions the cells were disposed in sheets, but elsewhere the tissue was irregular with some interlacing of cell bundles. Here the tissue appeared quite

compact. In many places giant cells of various types were abundant (Fig. 8*a*). Some were very large with an abundance of clear, very finely granular cytoplasm and one or two small nuclei. Others were large and irregular in outline with less cytoplasm and four to six very large, irregular nuclei which took the basophilic stain deeply. Mitotic figures were abundant. Degenerative changes were extensive and foci of liquefaction or granular degeneration in many regions caused pseudopalisading of the cells not unlike that seen in glioblastoma multiforme (Fig. 8*b*). The tissue was vascular, containing many well-formed, small vessels, some of which showed overgrowth of the vessel wall. Calcification or whorl formation was not observed. The tumor had no capsule other than a layer of compressed tumor tissue. Special stains disclosed no glia fibers other than those present as a result of invasion of the contiguous nervous tissue. Comparison of the tissue removed at the two operations revealed no essential difference in the microscopic appearance.

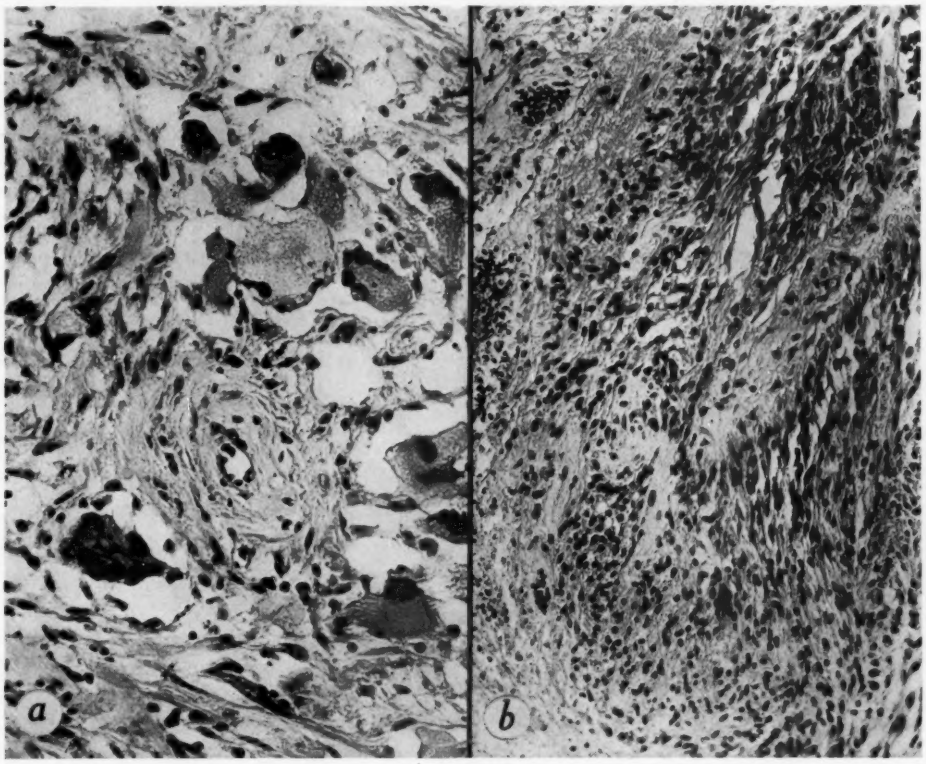

Fig. 8.—Case 13. Highly atypical malignant tumor which had many of the characteristics of glioblastoma multiforme in places, but which was of meningeal origin. *a*, To show the various types of atypical giant cells present (hematoxylin and eosin ×200). *b*, To show the cellularity of the tissue and the tendency toward pseudopalisading due to degeneration (hematoxylin and eosin ×130).

The general appearance of this tumor was not unlike that of glioblastoma multiforme with pseudopalisading of the cells, multinucleated giant cells, and overgrowth of the walls of the smaller vessels. However, closer inspection left no doubt as to the meningeal origin of the growth. The clinical course was much as was to be expected from the malignant appearance microscopically.

Case 14.—A large tumor measuring 10 cm. in diameter was removed from over the right frontal convexity in a 28-year-old woman. Symptoms had been present for three months and roentgenographic examination disclosed erosion of the frontal bone in the region of the growth. Microscopic examination showed the tumor to be

composed of moderately large, slightly elongated cells which were irregularly disposed, at times in columns and cords, between strands of connective tissue. The nuclei were somewhat irregular in shape and showed considerable variation in size (Fig. 9). In some regions invasion of the larger connective tissue strands by tumor cells was apparent. A coarse reticulum was present between the cells and cell groups. There were no giant cells, but mitotic figures were present in large numbers throughout the tissue. There was some evidence of invasion of the adjacent cerebral tissue, but from the surgical specimen this was not certain.

Fig. 9.—Case 14. Atypical, highly malignant tumor, probably of stromal origin, removed at operation. Note the irregularity of the tissue and the variation in cell and nuclear size. Mitotic figures are present (hematoxylin and eosin ×365).

COMMENT

The concept of the malignant tumor as an autonomous, invasive growth capable of giving rise to distant metastases requires some revision in respect to the malignant meningiomas and, indeed, in respect to most of the tumors arising within the cranial cavity. It is generally believed that intracranial tumors do not metastasize outside of the cranial and spinal chambers, and a survey of the literature discloses few instances in which an intracranial growth has given rise to a similar lesion outside of the nervous system. Nelson,[16] in 1936, was able to find in the literature for ten years prior to the publication of his article 7 reports of metastasizing intracranial tumors. Of these, 2 cases could be considered to fall within the group of meningeal tumors. Brandt,[17]

in 1934, reported briefly a case of "spindle-cell sarcoma of the dura" in the hypophyseal region in which death occurred four months following the appearance of the first symptom. At necropsy, three round, nodular, metastatic tumors were found in the liver, the largest the size of a walnut. The second case referred to was that reported by Foot and Zeek.[18] The patient was a 45-year-old man who died six weeks after the first symptom from a melanoma arising in the meninges of the right temporal region. At necropsy a dozen melanotic nodules were found in the lungs and the intracranial tumor was considered to be the primary lesion after a careful search had failed to disclose any other possible primary site. In both instances noted, operation had not been performed and irradiation had not been given.

Distant subarachnoid and intraventricular implants are not to be included under the heading of metastasis and should be looked on as "seeding," a process essentially different from the pathologic viewpoint. Such remote implantation of tumor is the result of the dissemination of viable tumor fragments by the cerebrospinal fluid and is frequently seen in medulloblastoma and choroid plexus papilloma and less frequently in other gliomas. In general, the property of giving rise to distant metastasis, which has been termed one of the cardinal properties of the malignant tumor, is rarely encountered in the meningeal growths, despite the degree to which other evidences of malignancy may be present. In none of the highly malignant tumors described here were there any associated secondary growths outside of the nervous system.

The general conception, frequently quoted in textbooks, is that the meningiomas rarely if ever invade the brain but rather compress it in the process of expansion. Nevertheless, Globus has stated, "It is necessary to correct at this point a statement made frequently that the meningioma never passes beyond the pial barrier and never penetrates the brain. In the large number of the tumors investigated in this study, the tumor had invaded the brain tissue to variable depths." This has also been found true in the present study. Reference must be made to the tendency noted by Cushing and others for meningiomas to recur after a variable time, despite what at the time of operation appeared to be a complete removal of the tumor. This indicates that many of these tumors are less encapsulated and less sharply defined from the adjacent cerebral tissue than would appear grossly, and reappearance of the growth must be considered as continuance rather than recurrence of the tumor. In certain instances, particularly if there has been piecemeal removal or if the tumor has been broken across in the process of removal, the meningiomas exhibit a tendency to seed in the adjacent muscle or scalp. Although this cannot be looked on as certain evidence of malignancy, it indicates a decided activity on the part of the tumor,

certainly not present in all the meningiomas. Cushing and Eisenhardt cited several instances of this, some of them in the variety which they described as malignant.

Oertell's[19] conception in reducing the factors of lawlessness and malignancy in cancer to terms of "intensity or tempo of growth" is particularly adaptable to the first group of tumors described here, those of low-grade or early malignancy. Craig, in his discussion of the malignant meningiomas, noted three stages in the metamorphosis of a benign to a malignant tumor: (1) hypertrophy of the cells, (2) hyperplasia or an increase of embryonic undifferentiated cells, and (3) the migration or invasion of the surrounding tissue by embryonic cells. He graded the tumors on the basis of cellular differentiation, mitotic figures, and the general tissue structure, and noted that in those meningiomas in which the grade of malignancy was low, whorl formation was observed. In the present study, whorl formation was seen infrequently in the first group and with rare exception it was absent in the tumors of advanced malignancy.

As Foot[20] has noted, the classification of the meningiomas based on the histologic nature of the tumors may be considered as variations in structure from the epithelioid type at one end to the purely fibroblastic or stromal variety at the other end. This conception of the meningiomas as compound tumors explains the variety of forms in both the benign and the malignant group in which either the parenchymatous or the stromal elements may predominate or compose the entire growth. It appears to be a characteristic of the malignant meningiomas that the composite makeup of the tumor tissue is lost or minimized with one of the elements, either the parenchymatous or the stromal, predominating in the final picture. Thus, malignancy appears to accentuate the type of growth whether it be of meningocytic origin, derived presumably from the arachnoid villi, or of stromal or fibroblastic origin, derived from the pia-arachnoid. In many instances, however, although one may predominate, remnants or indications of the association of the other may be found on careful examination.

The frequent bizarre and atypical forms which are encountered are to be considered as the progress of the anaplastic process beyond the stage of simple development of sarcomatous or malignant properties. The giant cells, frequently seen in the more malignant of the tumors described here, were considered by Globus as evidence of vigorous cell growth. Globus considered these cells as establishing a link between the meningiomas of quiescent type and those acquiring malignant character. It is to be noted that in many of the tumors of low-grade or early malignancy, early or incomplete forms of giant cells were noted.

Some mention must be made of the use of the term malignant meningioma in preference to the term sarcoma which might be applied to some of these growths. As far as can be determined at the present time,

these tumors of advanced malignancy do not differ clinically in their various types, but rather in their microscopic appearance. Inasmuch as they must be included under the group of meningiomas, it seems best to designate them as malignant meningiomas, indicating a specific variety with an essential origin from the meninges rather than as sarcomas, with which term the significance of their origin is lost. At the same time, the use of the descriptive term contrasts them with the ordinary benign variety of meningioma.

CONCLUSIONS

1. About 10 per cent of all meningeal tumors arising within the cranial cavity are microscopically malignant when judged by the type of cells, the architecture of the tissue, and the presence of giant cell forms and mitotic figures.

2. The malignant meningeal tumors may be divided into those which are of early or low-grade malignancy and those which are of advanced or high-grade malignancy. This differentiation is reflected in the changes in the architecture of the tissue in the low-grade malignant tumors and in the changes both in the cell type and structure and in the tissue architecture in the tumors of advanced malignancy.

3. The classification and differentiation of the various morphologic forms of these malignant tumors are based on the concept of these tumors as variations and admixtures of structural elements of two types. The epithelioid type of tissue forms one extreme and the fibroblastic or stromal type of tissue forms the other extreme. Thus, the tumors can be considered to be of parenchymatous or of stromal origin, and mixtures of the two types may occur in any one tumor.

4. Malignancy in these meningeal tumors tends to accentuate the character of the predominant type of tissue, whether it is of the parenchymatous or of the stromal variety.

5. Variations in structure in each of the types of the tumors of advanced malignancy are due in part to the anaplastic process with progression beyond that of simple malignant change.

6. The term malignant meningioma is to be preferred to the term sarcoma, which might be applied to some of these growths. The former indicates a specific variety of tumor with an essential origin from the meninges and contrasts these tumors with the ordinary benign meningiomas.

7. There is, in the main, a close correlation between the microscopic grade of malignancy and the clinical course when the duration of symptoms, size of the growth, and location are all taken into account.

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THROMBOANGIITIS OBLITERANS*

Clinical Observations and Arterial Blood Oxygen Studies During Treatment of the Disease With Sodium Tetrathionate and Sodium Thiosulfate

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IN THE treatment of thromboangiitis obliterans consideration should be given to the three factors in the pathology of the disease: (1) biochemical blood changes; (2) peripheral thromboses resulting in circulatory deficiency, infarcts, and gangrene; and (3) local infection. For the pathologic blood condition[1] we have used intravenous injections of sodium tetrathionate ($Na_2S_4O_6.H_2O$) and sodium thiosulfate ($Na_2S_2O_3.5H_2O$).[2] Pavaex treatment[3] is indicated for the circulatory deficiency resulting from arterial thromboses. Local infection of the peripheral tissues is usually treated with hypertonic (25 per cent) magnesium sulfate dressings. Because of the success in the treatment of thromboangiitis obliterans with the inorganic sulfur compounds some of our clinical observations and results of arterial blood oxygen studies are herewith reported.

The following cases illustrate the clinical course of the disease and the changes in the arterial blood oxygen which followed treatment. The patients were divided into two groups: (1) without infection and (2) with infection. Oscillometric and stabilized peripheral temperature readings were taken on all patients. Although the biochemical blood changes which followed treatment were fairly constant in the two groups, the clinical course differed because of the infection.

THROMBOANGIITIS OBLITERANS WITHOUT INFECTION

Case 1.—Mr. N., aged 23 years, of Norwegian descent, was first examined June 7, 1934, suffering with thromboangiitis obliterans of all four extremities of three years' duration. An excruciatingly painful ulcer about the size of a quarter on the right first toe had been present for three months. There was no infection. Constant rest pains and intermittent claudication (one-half block) had forced him to give up his work as a patternmaker. The oscillometric index of the right ankle and that of both wrists were almost zero (Fig. 1). He was a heavy cigarette smoker.

Biweekly injections of sodium thiosulfate were followed in six weeks by complete relief from rest pains and improvement in the intermittent claudication and ulcer. Despite the improvement and gain of thirty-five pounds in weight the temperature of the toes remained unchanged for more than two months. Pavaex treatment for

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the organic occlusion in the peripheral arteries was then started and was followed by rapid elevation in skin temperatures and the ulcer healed (Fig. 2). After periodically continuing biweekly injections for three years he has remained in excellent health without further treatment (four years) although he is still smoking moderately.

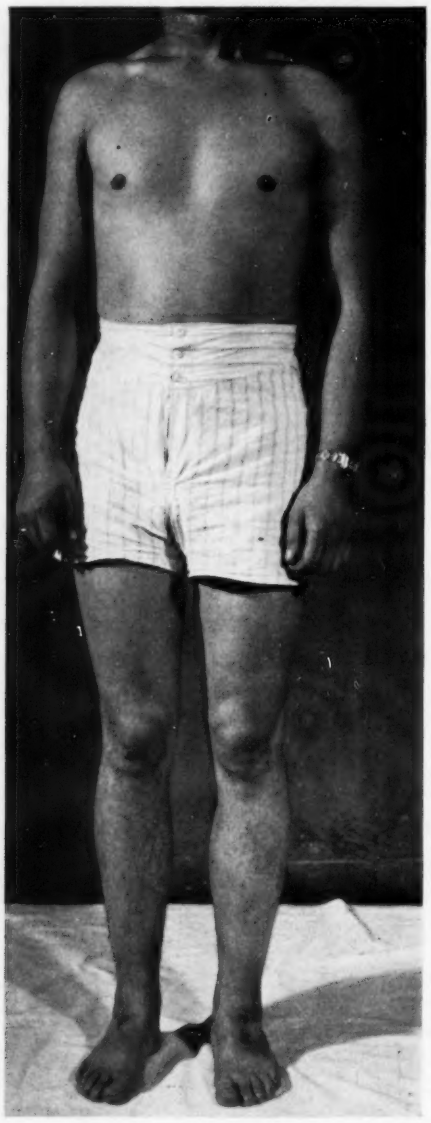


Fig. 1.—Patient clinically well for more than six years after treatment for acute thromboangiitis obliterans (Case 1). All four extremities were involved. Relief from the severe rest pains in the right foot and healing of a gangrenous infarct of the first toe were independent of changes in the peripheral temperatures (Fig. 2).

During the course of treatment the erythrocyte count varied from 4.4 to 7.5 millions and the hemoglobin index from 67 to 85 per cent. The normal relation between the colorimetric hemoglobin index and the oxygen capacity did not exist. After months of no treatment and of heavy smoking, an injection of sodium thiosulfate increased the oxygen capacity from 20 to 24 volumes per cent with an erythrocyte count of 5.7 millions and colorimetric hemoglobin value of 85 per cent remaining

unchanged. One year later when the patient was clinically well but still smoking moderately the effect on the oxygenation of the arterial blood of smoking two cigarettes was as follows:

	OXYGEN CAPACITY VOLUMES %	OXYGEN SATURATION %	CARBON-DIOXIDE CONTENT VOLUMES %
Arterial blood			
June 28, 1937: Receiving treatment, smoking moderately			
Before smoking	17.99	93.15	47.08
After smoking two cigarettes	17.22	88.00	46.92

Comment.—Clinical improvement with complete relief from rest pains and healing of a noninfected ulcer of the toe followed twelve biweekly injections of sodium thiosulfate. The peripheral skin temperatures remained unchanged for two months. Pavaex treatment rapidly elevated the temperatures to the normal level. While the patient was clinically well, although continuing to smoke moderately, the oxygen saturation of the arterial blood was reduced 5 per cent by smoking two successive cigarettes. This reduction did not occur in more than fourteen control patients but was observed in other patients with thromboangiitis obliterans.

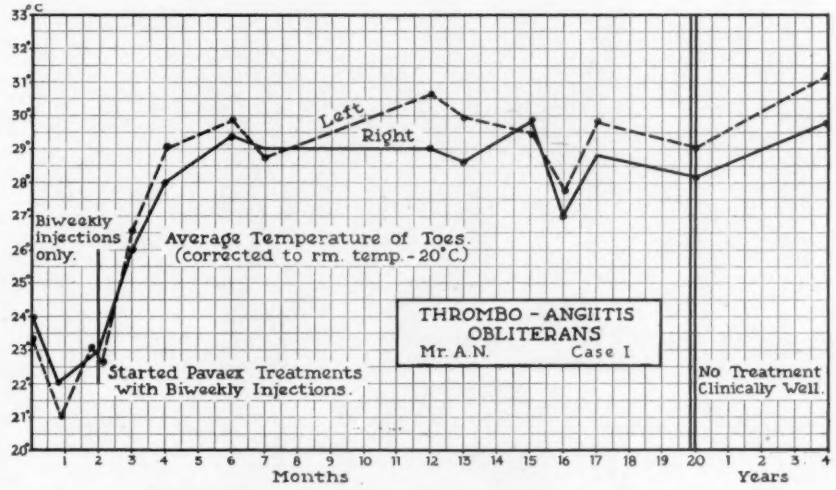


Fig. 2.—Complete relief from rest pains (Fig. 1, Case 1) followed treatment of the pathologic blood condition with biweekly injections of sodium thiosulfate for six weeks. Despite the marked clinical improvement the peripheral skin temperatures remained unchanged. Rapid elevation of skin temperatures followed pavaex treatment.

CASE 2.—Mr. M., aged 43 years, a Mexican freight handler, was admitted on Oct. 20, 1934, suffering with severe intermittent claudication (one block) and rest pains of the right leg. Since December, 1933, when he thought that he had frozen the right foot, the symptoms had become progressively worse. He had been a heavy smoker of Mexican cigarettes.

He remained in the hospital for four days but continued biweekly injections of sodium thiosulfate for six weeks. Complete relief from pain and elevation of skin temperatures followed treatment. Although he resumed heavy smoking he remained completely comfortable. He was then unable to return for three weeks

because of inclement weather. Two days before his readmission on Dec. 20, 1934, all the previous symptoms recurred and the right second toe suddenly became black and excruciatingly painful.

For two months other forms of treatment without the inorganic sulfur compounds were used without relief from pain. From 6,000 to 8,000 c.c. of Ringer's solution was given daily for four weeks. Badly infected teeth were extracted and bacterial filtrates of *Streptococcus viridans* were obtained and given intradermally

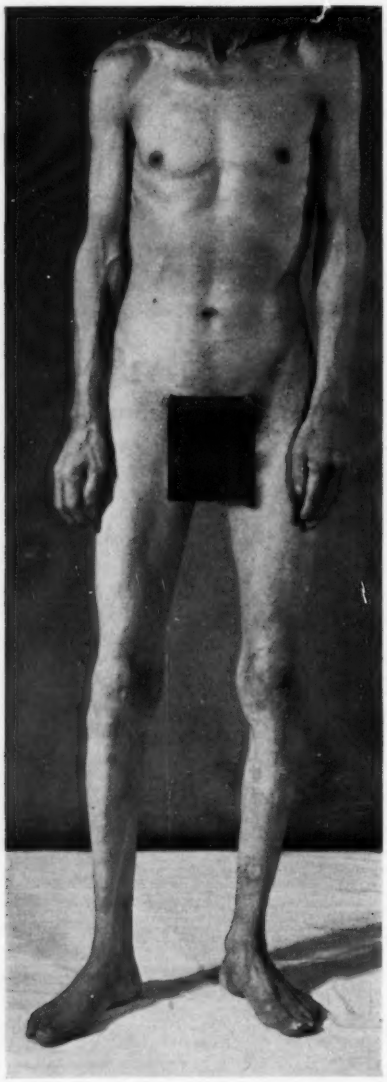


Fig. 3.—Patient clinically well (December, 1934) after numerous recurrences of gangrenous ulcerations. Despite increase in peripheral temperature of the toes of 6° C. following other forms of treatment for two months, relief from pain did not occur until two weeks after treatment with sodium thiosulfate was resumed (Case 2).

without effect. Despite the lack of subjective relief the peripheral temperatures increased 6° C. Prompt relief from pain followed daily injections of sodium thiosulfate for two weeks when the gangrenous toe was amputated. Complete recovery was rapid and he gained twenty pounds in weight (Fig. 3).

After resuming heavy smoking and discontinuing treatment for six months the disease recurred in both hands (Fig. 4) although the legs have remained in excellent

condition (six years). He is now enjoying fairly good health with periodic treatment although he has numerous finger deformities as a result of the disease.

The oxygen saturation of the arterial blood during a period of treatment and complete abstinence from smoking was considerably below the normal level. The initial effect of smoking was an increase in the oxygen saturation:

	OXYGEN		CARBON-DIOXIDE
	CAPACITY VOLUMES %	SATURATION %	CONTENT VOLUMES %
Arterial blood			
Jan. 27, 1938: Clinically improved, no smoking or treatment for some months			
Before smoking	18.66	80.95	49.91
After smoking one cigarette	18.27	92.12	49.56

Fig. 4.—Marked clinical improvement occurred after involvement of both lower extremities. Six months later, infected infarcts occurred in the fingers of both hands (Case 2) after resumption of heavy smoking and discontinuing treatment.

Comment.—The first acute attack of thromboangiitis obliterans with impending gangrene was relieved within six weeks by intravenous sodium thiosulfate. Recurrence followed discontinuance of treatment and resumption of heavy smoking. Other forms of treatment were then used for two months without relieving the severe rest pains despite increased peripheral temperatures of 6° C. The pains were relieved within two weeks after resumption of the inorganic sulfur therapy. While clinically well and not smoking the low percentage of oxygen saturation of the arterial blood was increased to the normal level (Table I) by smoking one cigarette. This initial effect was accompanied by elevation in blood pressure, increased pulse rate, and peripheral vasoconstriction. The systemic need for these responses may explain the almost uncontrollable desire of patients with thromboangiitis obliterans to smoke.

TABLE I

ARTERIAL BLOOD, OXYGEN CAPACITY AND OXYGEN SATURATION

	NO. CASES	NO. DETERMINATIONS	OXYGEN CAPACITY VOLUME PER CENT			OXYGEN SATURATION PER CENT		
			MAXIMUM	MINIMUM	AVERAGE	MAXIMUM	MINIMUM	AVERAGE
Controls	20	30	20.96	17.50	18.72	96.60	88.20	92.45
Males	15	22	20.96	17.50	18.91	96.60	88.20	92.29
Females	5	8	18.82	17.69	18.44	96.40	88.60	92.66
Thromboangiitis obliterans	22	48	21.50	11.00	17.46	101.30	54.70	88.49
No treatment { Not smoking (?)	6	8	18.96	14.20	17.10	81.20	54.70	74.28
No treatment { Heavy smoking	2	3	11.68	11.00	11.40	96.10	87.40	92.50
Neurocirculatory	11	29	20.00	14.52	16.72	98.70	79.40	91.00
Males	5	14	20.00	14.52	17.11	98.70	83.80	91.02
Females	6	15	17.36	14.70	16.26	96.90	79.40	91.01
Raynaud's disease	3	6	17.36	15.90	16.50	95.50	79.40	88.34
Arteriosclerosis	6	9	19.61	15.75	16.92	98.65	87.04	92.19
Polycythemia vera	1	4	25.50	22.20	22.90	99.36	75.90	83.99

CASE 3.—Mr. K., aged 48 years, a gentile grocery store clerk, was referred April 17, 1939, because of a previously diagnosed thromboangiitis obliterans of the left foot and leg. In May, 1937, the right leg was amputated elsewhere. Following resumption of smoking, pains, coldness, and discoloration developed in the left foot. Pulsations were palpable in the dorsalis pedis, posterior tibial and popliteal arteries. No treatment or further examination was made at this time.

He returned on July 27, 1939, with the arterial pulsations in the foot no longer palpable. Oscillometric index at the ankle was zero. The blood examination showed erythrocyte count of 4,550,000, hemoglobin index of 78 per cent, and leucocyte count of 7,450. These blood findings were associated with the following initial oxygen capacities of the blood:

	OXYGEN CAPACITY VOLUMES %	OXYGEN SATURATION %	CARBON-DIOXIDE CONTENT VOLUMES %
Arterial blood			
July 27, 1939:			
Before injection	11.00	96.10	45.80
After 0.6 Gm. sodium tetrathionate	11.70	87.40	44.30
Aug. 10, 1939: No treatment since July 27, 1939			
Before injection	17.60	96.10	44.70
After 0.6 Gm. sodium tetrathionate	17.60	90.30	43.90

Bi-weekly injections were continued for one month when he reported that he was feeling much better and had gained ten pounds in weight. It is doubtful that he had discontinued smoking.

Comment.—Clinical improvement which followed intravenous sodium tetrathionate was accompanied by marked increase in the oxygen capacity of the arterial blood. The initial oxygen capacity was far below the normal level. The colorimetric hemoglobin index and erythrocyte count remained unchanged despite the marked increase in oxygen capacity two weeks after one injection of sodium tetrathionate.

CASE 4.—Mr. H., aged 63 years, a retired American gentile salesman, was admitted Jan. 29, 1940, suffering with advanced bilateral thromboangiitis obliterans. Oscillometric readings of both lower legs were almost zero. Roentgenograms were negative for arteriosclerosis. He was an unusually heavy cigarette and pipe smoker. Biweekly injections of sodium tetrathionate were followed by marked improvement in the biochemistry of the blood and in the clinical symptoms. At the present time (February, 1941) he walks five to six blocks without distress and feels well.

The results of the blood oxygen studies were as follows:

	OXYGEN CAPACITY VOLUMES %	OXYGEN SATURATION %	CARBON-DIOXIDE CONTENT VOLUMES %
Arterial blood			
Feb. 14, 1940: Initial, new case, curtailed smoking 1 wk.			
Before injection	14.70	67.80	48.60
After 0.4 Gm. sodium tetrathionate	14.70	67.10	48.60
April 23, 1940: Biweekly injections	14.00	96.10	49.60
Oct. 31, 1940: Biweekly injections	14.67	94.20	47.00

The increased oxygenation of the arterial blood from 67 to 96 per cent was accompanied by marked improvement in the initially elevated blood sugar, cholesterol and cholesterol esters, total fatty acids, and low glutathione.

Comment.—Marked clinical improvement followed biweekly injections of sodium tetrathionate. The initial low percentage of oxygen saturation of the arterial blood increased to the normal level. The oxygen capacity remained unchanged and below normal for the colorimetric hemoglobin value which was present.

CASE 5.—Mr. B., aged 42 years, a gentile salesman, was admitted to the hospital April 17, 1939, suffering with bilateral thromboangiitis obliterans of both lower extremities. For years he smoked two to three packages of cigarettes daily and he was a heavy drinker. Daily injections of sodium tetrathionate and pavaex treatment resulted in relief from pain within three weeks. This was accompanied by rapid improvement in the sedimentation time of the blood (Table II).

TABLE II

	TIME FOR 18 MM. OF CELLS (LINZENMIER METHOD)	REMARKS
April 18, 1939	25 min.	Intensive treatment ($Na_2S_4O_6.H_2O$) started
April 19, 1939	30 min.	
April 24, 1939	30 min.	
April 29, 1939	35 min.	
May 6, 1939	1 hr. 15 min.	
May 14, 1939	2 hr. 55 min.	Normal values
May 21, 1939	4 hr. 25 min.	
June 10, 1939	6 hr. 10 min.	
July 22, 1939	4 hr. 30 min.	
Nov. 3, 1939	1 hr. 20 min.	Resumed heavy smoking; recurrence
Dec. 2, 1939	1 hr. 20 min.	
Jan. 24, 1940	6 hr. 00 min.	Intensive treatment ($Na_2S_4O_6.H_2O$)
Feb. 2, 1940	4 hr. 00 min.	
Feb. 24, 1940	4 hr. 30 min.	
March 25, 1940	6 hr. 35 min.	

The oxygenation of the arterial blood was as follows:

	OXYGEN CAPACITY VOLUMES %	OXYGEN SATURATION %	CARBON-DIOXIDE CONTENT VOLUMES %
Arterial bloods			
April 19, 1939: Initial, heavy smoker	14.29	81.20	47.10
Smoked two cigarettes	14.36	87.10	45.70
Smoked four cigarettes	14.61	86.20	46.40
July 22, 1940: Bi-weekly injections			
Before injection	20.00	91.40	38.50
After 0.6 Gm. sodium tetrathionate	20.20	94.20	39.00

Comment.—Marked clinical improvement with complete relief from rest pains followed three weeks' treatment with sodium tetrathionate. The initial low percentage of oxygen saturation and oxygen capacity increased to the normal levels. The gradual improvement in the initial rapid sedimentation rate of the blood during treatment is shown in Table II. There was no ulceration or infection present.

THROMBOANGIITIS OBLITERANS WITH SECONDARY INFECTION

Bacteriologic studies of smears and cultures obtained from ulcerated or infected areas failed to account for the unusual features of these infections. A number of aerobic organisms were present either in pure culture or in a mixed infection. No anaerobic growths were obtained. *Streptococcus viridans* and *Staphylococcus aureus* were most frequently found, although organisms of Escherichia, Pseudomonas, *Staphylococcus albus*, and Corynebacterium groups were occasionally present. An excised thrombosed dorsalis pedis artery (Case 1) did not produce bacterial growth on a number of culture media.

CASE 6.—Mr. L., aged 46 years, a Russian Jew, was first examined March 4, 1940, having suffered with bilateral thromboangiitis obliterans of the lower extremities since 1930. During the ten-year period he had elsewhere bilateral cervical and lumbar sympathectomy and nine peripheral nerve operations. Amputation of the right leg was refused and he came to us for treatment. For more than twenty-five years he had consumed more than two packages of cigarettes daily.

On admission to the Presbyterian Hospital he was bedridden with an infected ulcerated right foot and first toe (Fig. 5). Extreme unremitting rest pains were present for weeks. Six weeks of daily injections of sodium tetrathionate were followed by marked improvement in the pain and infection. On April 17, 1940, a wedge-shaped resection of the toes was performed because of extensive osteomyelitic destruction of the bones. He was discharged on April 29, 1940, and periodically since then he has received biweekly injections and pavaex treatment (Fig. 6). Although the operative wound was slow in healing and he sometimes has burning pain in the healed first toe, he is now active and enjoying fairly good health (one year).

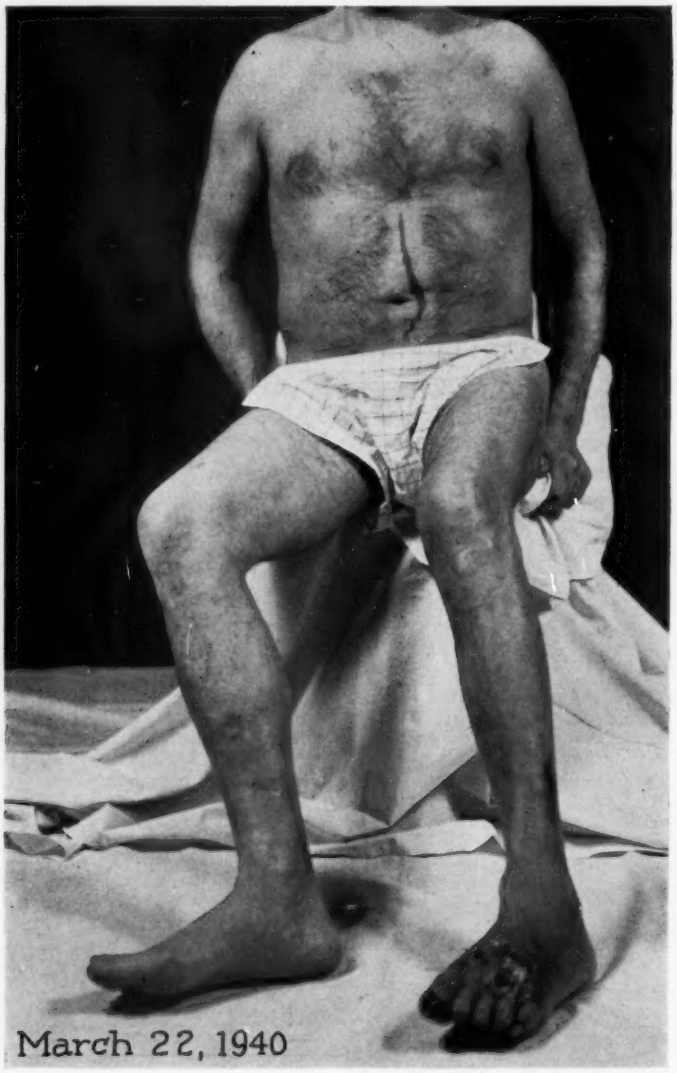
Arterial blood oxygen determinations were made four months after discontinuance of smoking and treatment:

	OXYGEN CAPACITY VOLUMES %	OXYGEN SATURATION %	CARBON-DIOXIDE CONTENT VOLUMES %
Arterial blood			
Oct. 17, 1940: No treatment or smoking for 4 mo.			
Before injection	17.55	54.70	51.20
After 0.6 Gm. sodium tetrathionate	18.96	67.10	38.50
Dec. 5, 1940: Biweekly injections of sodium tetrathionate	17.36	90.30	39.80
Dec. 19, 1940: No treatment 2 wk.	16.20	90.50	45.90

Comment.—Marked clinical improvement followed sodium tetrathionate therapy in a patient with infected gangrenous ulceration of the foot. Elsewhere cervical and lumbar sympathectomies and multiple peripheral nerve resections were performed over a ten-year period without affecting the course of the disease. Following his refusal of amputation the patient came under our care. After clinical improvement occurred and no treatment had been given for four months, arterial blood oxygen studies

were carried out. The initial percentage of oxygen saturation was unusually low but increased to normal after intravenous therapy.

CASE 7.—Mr. B., aged 27 years, a Lithuanian gentile electrician, was admitted to the hospital March 13, 1936, having suffered for one year with thromboangiitis obliterans of both lower extremities. There were infected gangrenous ulcerations of the left first, fourth, and fifth toes and adjacent portion of the foot. He was a heavy cigarette smoker.



A.

Figs. 5 *A* and *B*.—Clinical recovery from infected gangrenous ulceration of right foot followed treatment. Previously, cervical and lumbar sympathectomies and multiple peripheral nerve operations had been performed elsewhere (Case 6). *A*. Before treatment. *B*. After treatment.

Daily injections of sodium thiosulfate were followed by relief of pain within six weeks, but spontaneous amputation of the three gangrenous toes and healing of the wound did not occur for three months. Because of the infection, pavaex treatments were used cautiously and infrequently. Four months later he returned to work.

Almost two years later on Aug. 31, 1938, he was readmitted with infection of the remaining toes of the left foot. Injections of sodium tetrathionate and pavaex treatments resulted in sufficient improvement to permit his discharge Oct. 12, 1938. He then resumed heavy smoking, but his condition continued to improve and he returned to work in January, 1939. In February, his foot again gave him trouble and he was refused further treatment because he would not stop smoking. Amputation of the leg was then performed elsewhere and he remained in the hospital for nine months without the wound completely healing.

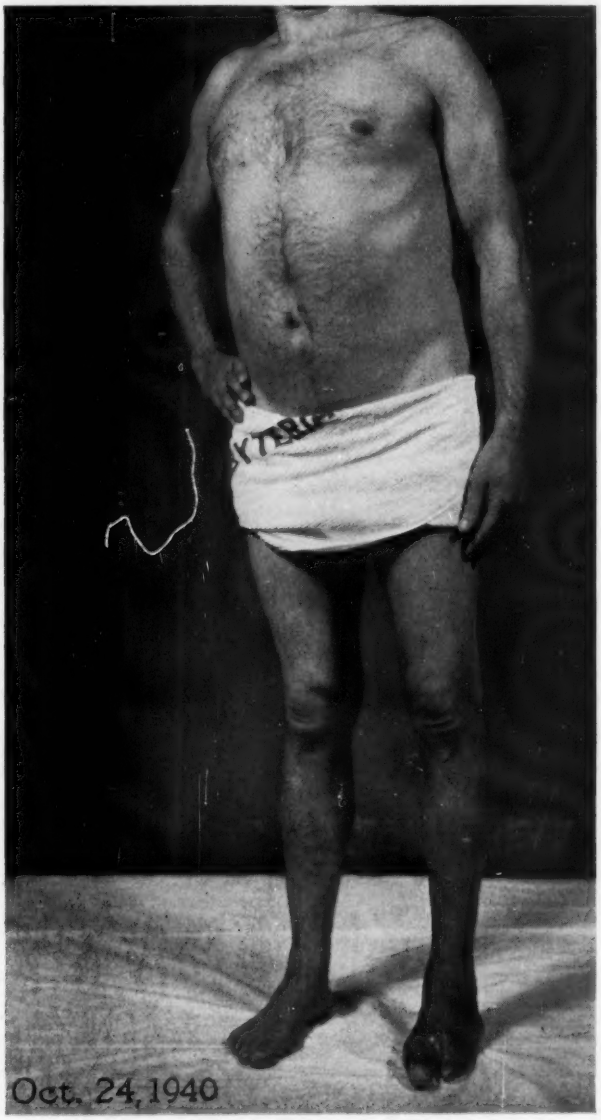


Fig. 5*B*.—See opposite page for legend.

In May, 1940, he returned to us for a checkup and was told again to stop smoking. On Dec. 26, 1940, he returned with a marked involvement of both hands and the right (remaining) foot, but no infection or gangrene. Clinical improvement followed biweekly injections of sodium tetrathionate for three weeks. The initial

oxygen saturation of the arterial blood (femoral artery) of 81 per cent was increased to 92.4 per cent following the first injection. The clinical improvement was accompanied by an increase in the sedimentation time from one hour to six hours (Linzenmier method).

Comment.—Complete recovery followed two serious attacks of infected gangrenous ulcerations of the foot. With the third recurrence, amputation was performed elsewhere. Two years later both hands and the remaining foot became involved and the patient returned to us for treatment. Marked clinical improvement was accompanied by a normal percentage of oxygen saturation of the arterial blood and by normal sedimentation time.

A.

Figs. 6 *A* and *B*.—Clinical recovery from two serious attacks of infected gangrenous ulcerations of foot followed treatment (Case 7). Amputation was performed elsewhere because of a third recurrence. Recently the patient returned to us for treatment with both hands and the remaining foot involved. *A*. Before treatment. *B*. After treatment.

CASE 8.—Mr. N., aged 35 years, a gentile automobile mechanic, suffered with progressively severe symptoms of thromboangiitis obliterans for eight months prior to the development of gangrenous ulcerations of the second, third, and fourth toes.

He was admitted to a hospital elsewhere where he refused amputation and was discharged.

He was admitted to the Presbyterian Hospital on April 26, 1937, with a foul-smelling, moist gangrene of the three lateral toes and a patch on the second toe of the right foot. The distal third of the dorsum of the foot was purplish red. Arterial pulsations were absent and the oscillometric index was 0.3 unit at the right ankle and 1.5 units on the left ankle.

Fig. 6*B*.—See opposite page for legend.

Daily injections of sodium tetrathionate were continued for one week when he was discharged from the hospital. He then continued biweekly injections and pavaex treatment as an ambulatory patient. Spontaneous amputation of the lateral three toes was followed by rapid healing of the wound. Within three months after treatment was started he returned to his work as a mechanic. He has continued in

excellent health (four years), but at his own request he still is receiving bimonthly injections of sodium tetrathionate. A recent arterial blood oxygen analysis was normal:

	OXYGEN CAPACITY VOLUMES %	OXYGEN SATURATION %	CARBON-DIOXIDE CONTENT VOLUMES %
Arterial blood			
Jan. 23, 1941: Complete clinical recovery			
Before injection	21.50	92.60	43.60
After 0.6 Gm. sodium tetrathionate	21.50	93.30	42.50

Comment.—Rapid and complete recovery of a patient with infected gangrenous ulcerations and thromboangiitis obliterans followed treatment with sodium tetrathionate. The oxygen capacity and oxygen saturation of the arterial blood is now normal and he is enjoying excellent health.

Fig. 7.—Rapid and complete clinical recovery (four years) from infected gangrenous ulceration of foot, followed intravenous sodium tetrathionate and pavaex treatments (Case 8).

Method of Investigation.—Methods and procedures were the same as described in our previous publications.[13, 14, 18, 19] Except where indicated, arterial blood was obtained from the right radial artery.

Method of Treatment.—Prior to 1937, only sodium thiosulfate ($Na_2S_2O_3.5H_2O$) was available for treatment of the pathologic blood condition. Since then we have had prepared sodium tetrathionate ($Na_2S_4O_6$.

H_2O)* which we found to be slower in action but more prolonged in its effect than sodium thiosulfate.[14] The tetrathionate is not as rapidly eliminated in the urine as free sulfate as is the thiosulfate.

In acute cases when the immediate effect of the medication is desirable, we alternate daily injections of the thiosulfate with the tetrathionate. As the acute stage subsides we continue periodic biweekly or weekly injections of the sodium tetrathionate solution. The usual intravenous dosage which we have been using is 1 Gm. of the sodium thiosulfate and 0.4 or 0.6 Gm. of the sodium tetrathionate dissolved in 10 c.c. of sterile distilled water. Transitory reactions may occur with either drug, but as a rule they are relieved by drinking a glass of water. We have observed no serious reaction in almost 8,000 injections. The appearance of the blood and an occasional sedimentation test are usually sufficient evidence as to the course of the disease.

Pavaex treatments are used for deficient circulation due to thrombotic occlusion of the peripheral arteries. These treatments, competently and adequately given, are beneficial in improving the peripheral circulation. In completely recovered patients all treatment may be discontinued, but when smoking has been resumed, periodic injections should be continued.

COMMENT

The clinical results in the treatment of more than sixty patients with thromboangiitis obliterans have been most encouraging, especially in view of the heretofore poor prognosis of the disease.[21] We have observed numerous recurrences, but in every case smoking had been resumed and it was possible that the treatment had been inadequate or prematurely discontinued. In the past seven years, six patients had minor surgical procedures and one required major amputation because of extension of serious secondary infection. Another patient after a third recurrence of the disease had a major amputation elsewhere, but he returned to us two years later with both hands and the remaining foot involved. Neither amputation nor sympathetic nerve operations had changed the course of the disease in the patients whom we have observed. Our clinical results are in sharp contrast with those of Horton and Brown[22] who reported the eventual loss of one or more limbs in 20 to 30 per cent of the patients and who, like Homans[23] and de Takats and Reynolds[24] reported amputations for relief from intractable pain.

The most constant chemical blood change which we detected was a deficient oxygenation of the arterial blood in the active stage of the disease (Table I). The percentage of oxygen saturation was especially low after smoking had been curtailed or discontinued and was accompanied by low blood pressure and by a slow pulse rate. The unusually low oxygen capacity in some acute cases occurred after heavy smoking. Some patients with thromboangiitis obliterans had erythrocyte counts

*Sodium tetrathionate has been prepared for us experimentally and supplied by G. D. Searle & Co., Chicago.

from 4.5 to 6 millions and colorimetric hemoglobin values of 75 to 95 per cent with abnormally low oxygen capacities. The normal relation between the oxygen capacity and the colorimetric hemoglobin value[25] usually returned after treatment with sodium tetrathionate or sodium thiosulfate and with clinical improvement.

Clinical improvement accompanied the increased oxygenation of the arterial blood, but from two to six weeks were usually required for complete relief from rest pains. This delay was probably due to the time required for readjustment in the systemic pathophysiologic changes which resulted from the low oxygenation of the arterial blood during the active stage of the disease. Although fairly normal oxygenation of the arterial blood may be present after the first few injections of the inorganic sulfur compounds, it seemed advisable to continue the treatment for many months. Smoking should be permanently discontinued, but it has been our experience that smoking was resumed by the large majority of these patients despite all advice and personal experience to the contrary.

CONCLUSIONS

The clinical results in the treatment of the biochemical blood changes in acute or active thromboangiitis obliterans with sodium tetrathionate or sodium thiosulfate and of the peripheral circulatory deficiency due to arterial thromboses with pavaex treatment have been most encouraging.

Deficient oxygenation of the arterial blood was usually present during the active stage of the disease. Following treatment for two to six weeks, the increased oxygenation of the arterial blood was accompanied by clinical improvement and in some cases by clinical recovery (five years).

The oxygenation of the arterial blood in the majority of patients with thromboangiitis obliterans which we studied was affected by smoking.

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Recent Advances in Surgery

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THE PROPHYLAXIS OF PERITONEAL ADHESIONS

A REVIEW OF THE LITERATURE

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FOREWORD

THE peritoneal adhesion has been recognized as a surgical entity for nearly 150 years, its etiologic factors and pathologic characteristics have been understood for over 50 years, and, yet, no satisfactory major prophylaxis has been developed. After seeing successive operations for lysis of intra-abdominal adhesions followed so frequently by an increased incidence of adhesion formation, it is no wonder that many surgeons have acquired a hopeless attitude toward there ever being found a satisfactory method of prevention. Years ago Hertzler[69] aptly expressed this attitude when he remarked: "This sequence lasts as long as the patient does, or the hopeful persistence of the surgeon endures." This surgical enigma constitutes a constant professional challenge and a justification for periodic consideration of the subject.

Duff[42] tabulated for several years at McGill University the incidence of all adhesions, significant and insignificant, observed during the course of routine autopsy examination and found that 30 per cent of cases without previous laparotomies presented adhesions. The incidence of adhesions in cases with previous abdominal operations is high. Naegeli[119] examined by pneumoperitoneum 148 cases with previous laparotomies and found that 80 to 90 per cent of them had x-ray evidence of intra-abdominal adhesions. He then operated upon these cases (for old and new diagnoses) and observed that 80 per cent presented adhesions of some kind. Duff[42] encountered peritoneal adhesions at routine post-mortem examinations in about 90 per cent of cases with a history of previous abdominal operations. Payr[130] stated that in all major laparotomies some 3.5 per cent are performed for the relief of intestinal obstruction from any cause. Of these, according to Christopher[19] and Rockwell,[150] 30 to 40 per cent are due to peritoneal adhesions.

Fortunately, most intra-abdominal adhesions resulting from healing by fibrosis cause no harm, but in a small percentage of cases surgical

intervention will be required for complications. These are: (1) visceral obstruction; (2) visceral dysfunction due to distortion or displacement of an organ; (3) persistent pain probably through attachment to and traction on the abdominal parieties. Most modern surgeons operate rarely for the last two of these complications. The surprisingly high incidence of peritoneal adhesions, the hazards of intestinal obstruction, the difficulties of operative treatment when obstruction occurs, and the notorious tendency for adhesions to re-form often in greater number than before, all combine to emphasize the importance of the prophylaxis of peritoneal adhesions.

There is one factor in the problem that has received little consideration; namely, the apparent tendency of some individuals to develop adhesions as compared to others. Plastic surgeons are aware of the fact that equally good scars cannot be obtained in the closure of comparable wounds in all individuals. Lehman[95] has seen unexpected intraperitoneal adhesion formation in patients presenting keloidal abdominal scars. Many extensive peritoneal infections will be followed by practically no adhesions; whereas, the simplest sort of abdominal intervention may result in extensive adhesions. Whether these variations are the result of a "fibroplastic diathesis," hereditary or dietetic (vitamin) in origin, or whether they result from unrecognized defects in surgical treatment, such as undetected residual chronic infection,[115] cannot now be stated. They deserve further investigation.

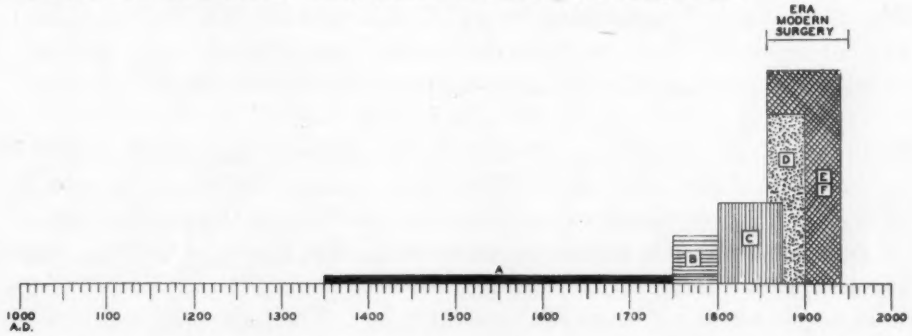

Fig. 1.—Historical development of knowledge of adhesions through Gay's six periods. *A.* Adhesion symptomatology established (1350-1750). *B.* Adhesion symptomatology related to structural changes (1750-1800). *C.* Structural changes related to disturbed function (1800-1870). *D.* Causative agents of peritonitis established (1860-1900). *E.* Relief of adhesions (1860 to present). *F.* Prophylaxis of adhesions (1860 to present).

HISTORY

In the development of the knowledge of disease, Gay and his associates[50] have pointed out that medical progress first established (1) *symptomatology;* then, it progressed to (2) the related *structural change* which explains the symptoms; (3) the *pathologic process* that precedes and produces the structural change; (4) the *causative factors* which start the process; (5) the *relief* or *cure;* and, finally, (6) *prophylaxis* or

prevention. This historical sequence in relation to peritoneal adhesions will be briefly presented (Fig. 1).

Establishment of Symptomatology of Adhesions (1350-1750).—The establishment of the obstructive symptomatology of peritoneal adhesions did not occur until near the end of the seventeenth century. It was a slow progress with many setbacks.

During ancient and medieval days there was only one disease but many symptoms.[50, 102] Abdominal maladies were considered due to some ailment of the peritoneal lining, or "sacred sac." To a reactionary, epidemic and individual instances of abdominal disease were associated with disfavor on the part of the Deity or with demoniac possession. Were one a liberal thinker believing in the Greek and Roman conceptions of disease, as embodied in the writings of Hippocrates and Galen, all abdominal complaints were accounted for by faulty mixtures of the four "humors."

By the time of the Renaissance (1450-1650), however, physicians gradually differentiated symptomatically between three "belly passions."[16] For the first time the acute abdomen was no longer considered a single disease with varying symptoms; it was recognized that numerous differing diseases might occur. The "renal passion" we now know to be calculous kidney colic; the "iliac passion" is now described as peritonitis; the "colic passion" we now recognize as intestinal obstruction, so frequently caused by peritoneal adhesions. Carson[16] credits John of Goddesden in the Rosa Anglica in 1314 as one of the first physicians to record such a clinical differentiation, and Sydenham in 1788 as perhaps the last. Thus, the obstructive symptomatology associated with peritoneal adhesions was established.

Relating of Symptoms to Structural Changes (1750-1800).—After a long period of professional subjection to metaphysical and theological authority, a great advance came through the correlation of structural change with symptomatology. The establishment of the medical school at Bologna in 1260 was associated with the beginning of regular postmortem examinations.[50] Morgagni, in his *De Sedibus et Causis Morborum,* gave the world in 1761 the first complete account of lesions of the body, carefully correlated with the clinical history of the patient and based on first-hand information.[50] It is not surprising, then, to find that shortly thereafter the peritoneal adhesion was definitely established for the first time as a true disease entity. Three physicians were largely responsible for these initial studies.[16] They were: John Hunter (1728-1793), London surgeon and anatomist; Marie François Xavier Bichat (1771-1802), Parisian physician extraordinary and inventor of the stethoscope; and René Laënnec (1781-1826), a surgeon and anatomist of the period following the French Revolution. In 1802 Bichat published the first famous work on peritonitis and its resulting adhesions which revolutionized the concepts of intra-abdominal disease in general and of peritoneal disease in particular. Of the three men,

Hunter concerned himself most with peritoneal adhesions, carefully describing their gross aspects and intelligently ascribing them to peritonitis. The true causative agents or factors of peritonitis were unknown then, but Hunter described three common clinical causes of peritonitis frequently observed to produce adhesion formation. He named the sticky substance holding the bowel surfaces together "gluten."[21, 60]

Relation of Terminal Structural Change to the Underlying Pathologic Process (1800-1870).—From 1800 to 1870, due to the increasing incidence of autopsy examinations and improvements in the microscope, not only was gross peritonitis established as the essential pathologic process producing peritoneal adhesions,[16, 21, 114] but also the common clinical causes of peritonitis were discovered and recorded.[16, 21, 114] In rapid succession appendicitis, puerperal fever, subphrenic abscess, gastrointestinal perforations, pelvic inflammatory disease, blood from ectopic pregnancies and other causes, cholecystitis, etc., were described as the producers of adhesions. Physicians of this period knew what the gross appearances of peritonitis and of peritoneal adhesions were, but they knew essentially nothing about the microscopic appearances and the bacterial and other inflammatory etiologies.

Establishment of the Causative Agents of Peritonitis (1870-1900).—The epochal advance of the next period rests upon two scientific accomplishments, the birth of bacteriology and the maturation of modern surgical principles. Fresh, nonnecrotic pathologic material was now obtainable for study, and it was possible for surgeons to observe the course of an abdominal disease before it reached the terminal state seen at post-mortem examination, and to identify and record offending bacteria.

Promptly the master pathologists of this era demonstrated the pathologic events in the formation of adhesions and observed that such adherences are generally caused by one of the four cardinal types of inflammation (traumatic, bacterial, thermal, and chemical).[53, 147, 152, 153, 167, 173] In 1887 Weigert developed a specific stain for Hunter's "gluten" which was thereafter known as "fibrin."[21, 60]

Cure of the Symptoms Caused by Adhesions (1850-1941).—The only relief for offending peritoneal adhesions is their division. Operative lysis of adhesions was first proposed and practiced to some extent during the early and middle 1800's. One of the earlier references to such operative interference is an English record mentioned by Carson.[16] Britton, a physician to the Royal Free Hospital in London, during a discourse there in 1859 discussed operation for intestinal obstruction caused by bands and twists. He must have reflected contemporary medical opinion on operative intervention for intestinal obstruction in his illuminating remark: "Our wonder at the happy audacity of the operator is unaccompanied by any wish or hope of imitating his procedure." The modern developments in the surgical treatment of in-

testinal obstruction from adhesions will be discussed only as they relate to prophylaxis of re-formation.

Prevention of Peritoneal Adhesions (1860-1941).—The survey of the various measures which have been proposed to date for the prevention of the formation or re-formation of peritoneal adhesions represents the major province of this review.

PATHOLOGY OF ADHESIONS

There are three possible terminations to peritoneal inflammation, just as there are to inflammation involving other tissues: (1) death of the host, (2) resolution, (3) suppuration and necrosis with repair by fibrosis.

In the peritoneum the crucial structure in the determination of healing by resolution or by fibrosis is the mesothelium.* It is probable that peritoneal injury will end in resolution if there is no mesothelial destruction, or if damage is limited to the serosal cells themselves.[11, 31, 41, 69, 92] This termination implies a relatively mild inflammation and vigorous and prompt defense responses. Initially there are present fibrinous adhesions where the peritoneum is damaged. In infection, the effect is to limit temporarily the spread of the inflammation until it can be conquered by the defense mechanisms. When the body defenses have overcome the infection, the fibrin and cellular debris are removed by the phagocytic cells, the adhesion separates, and the inflammation rapidly resolves with re-formation of the mesothelium. Every experienced surgeon has encountered at operation a mass of fresh adhesions which at a later laparotomy are found to have disappeared entirely. The mesothelium in these instances was probably intact, or but slightly damaged, and there was no overgrowth of subperitoneal connective tissue resulting in organization between apposed surfaces. Though without initial fibrinous adhesions every local peritoneal infection might become general, and every perforation might prove fatal, such adhesions still do not represent the real surgical problem.

The second general type of peritoneal healing results by fibrosis in adhesions which may demand later surgical intervention. Fibrous peritoneal repair occurs when the inflammatory process has passed the stage where resolution is possible; i.e., where there is actual destruction of the serosa and damage to subserosal connective tissue.[1, 17, 32, 69, 92, 168] Under these circumstances organization of the fibrinous scaffolding begins and proceeds in an orderly sequence to the end stage of white scar of which the mature adhesion consists. Fibrotic repair may evidence itself in one of two ways. There may be healing without loss of substance (primary intention), or healing with loss of substance (sec-

*No reference could be found giving the average thickness of the various layers of the wall of the human bowel. A 7 μ thick hematoxylin-eosin microscopic section of the human jejunum was obtained and the various layers of the bowel wall were measured under high power with a special micron scale. The following measurements were obtained: serosa (peritoneum), 0.3 μ; subserosa (connective tissue), 6 μ; muscle layers, 48 μ; submucosa, 18 μ; and mucosa, 64 μ.

ondary intention).[17, 69, 82] In repair by primary intention the fibroblasts unite the opposing surfaces without any loss of tissue except for the mesothelium. This process presumably results in direct contact of the adherent surfaces. In repair by secondary intention the mesothelium, the damaged subperitoneal connective tissue, and sometimes portions of the muscle wall are replaced by a fibrotic scar. These cicatrices are frequently bandlike adhesions.

The chronological development of the formation of fibrous adhesions can be summarized as follows:[28, 69, 82, 147] (1) There is initial injury to the serosa and subserosa; (2) a serous or seropurulent exudate is promptly poured out at the sites of damage; (3) within a short time this exudate coagulates, forming fibrin; (4) the surfaces of adjacent organs adhere by means of the sticky fibrin coatings; (5) unless this fibrin is removed, or the fibrinous adhesions are kept apart by some means until healing has occurred, organization will proceed over the fibrin scaffolding, resulting eventually in a fibrotic peritoneal adhesion.

POSSIBLE METHODS OF ADHESION PROPHYLAXIS

From the consideration of the pathology of adhesions it is evident that there are five possible fundamental attacks to be directed toward their prevention. These are: (1) to limit or prevent initial peritoneal injury; (2) to prevent the coagulation of the serous exudate; (3) to remove or dissolve the deposited fibrin; (4) to keep apart the fibrin-coated peritoneal surfaces until mesothelialization has occurred; (5) to inhibit the fibroblastic proliferation once established.

A survey of the literature on the prevention of peritoneal adhesions suggests that it is possible to classify all proposed antiadhesion measures under one of these five headings. The historical sequence of attempts to prevent adhesions naturally does not follow the sequence of pathologic events. In order to clarify the present status of the prophylaxis of adhesions, the various methods proposed and presented in the literature will be discussed under headings corresponding to the above pathologic classification, presenting the various groups roughly in the inverse order of their importance or promise. An exception is made of the section dealing with the most important factor of all; namely, the prevention of the initial injury which starts the whole process. Inasmuch as limitation of trauma and contamination is an established surgical principle underlying and accompanying all other attempts to prevent adhesions, the consideration of methods of minimizing peritoneal damage is placed first.

I. THE LIMITATION OF PERITONEAL INJURY

The importance of the limitation of peritoneal injury as the chief attack against the formation and re-formation of peritoneal adhesions needs no emphasis. It is obviously and logically based on the pathologic

processes of adhesion formation just reviewed. With few exceptions its development stems from the contributions of surgeons writing between 1890 and 1910. (Fig. 2.)

Limitation of Mechanical Peritoneal Injury.—Traumatic injury to the peritoneum results from rough handling of tissues and organs at operation. Although the urgency of speed in operating may at times make a degree of excessive trauma unavoidable, yet all surgeons are in agreement that such trauma is to be avoided whenever possible in order not only to limit the formation of adhesions, but also to minimize the likelihood of infection and surgical shock.[54, 63, 84, 116, 136, 147, 167, 173, 176]

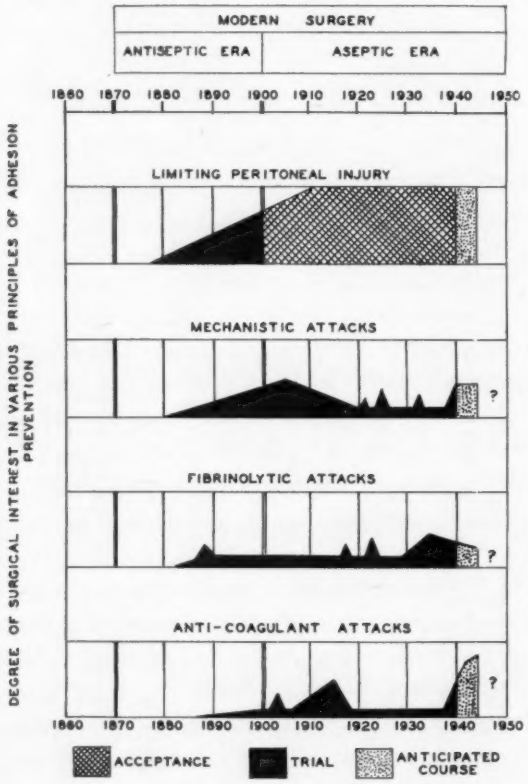

Fig. 2.—Schematic representation of historical course of development of methods of adhesion prevention.

Common transgressions against gentleness in handling the peritoneum might be listed as follows: (1) the unintelligently vigorous use of retractors; an incision one inch longer may spare the peritoneum much punishment; (2) mauling of the bowel surfaces by the introduction of large and numerous gauze pads to facilitate exposure; (3) application of dry gauze which adheres and when removed often brings away the mesothelium; (4) unnecessary sponging, as a sort of surgical tic; (5) the use of large hemostats in controlling bleeding, and the employment of mass ligatures (see below); (6) the failure to peritonealize denuded

surfaces; (7) the use of unnecessarily large needles and sutures, their rough passage through the tissue, and the leaving behind of unnecessarily long cut suture ends (see below).

Hemostasis.—The standard methods of hemostasis by ligature properly applied need no discussion here except to stress the continued validity of Halsted's precepts.[62] There has been recently presented, however, a hemostatic method to be employed in operations for adhesions which deserves mention.

Following earlier scattered observations,[53, 148, 165, 167, 176] the use of cautery tissue coagulation in the peritoneum was revived by Reichert, Gerbose, and Halford.[143] This method may be applied either by the live cautery or by electrocoagulation. The rationale of its use is expressed as follows: After a small eschar is formed, exudation ceases from its surface. Healing then takes place beneath its base and when it separates the peritoneal surface is already reconstituted. Reichert and his coworkers demonstrated experimentally that adhesions so divided did not re-form. Inasmuch as other adhesions secondary to the operative intervention did form, this method does not fundamentally attack the problem of the prophylaxis of adhesions. It may be useful, however, in conjunction with other methods.

In relation to hemorrhage a recent report by Joseph[81] must be mentioned. He believes on the basis of clinical observations made during the recent civil insurrections in Palestine, and on the basis of subsequent animal experiments which are not given in detail, that the introduction of fresh whole blood into the peritoneum after contamination prevents postoperative peritonitis and peritoneal adhesions by augmenting antibodies and leucocytes. These findings are opposed to general clinical experience with wound hematomas and to experimental studies. Allen[2] (1927) demonstrated a diminished resistance to infection of the pleura when blood was introduced together with a contaminant. Intraabdominal hemorrhage has been commonly considered a cause of adhesions, and at operation performed some days after such hemorrhage, adhesions are found. Joseph's work can be accepted only after confirmation.

Limitation of Bacterial Peritoneal Injury.—The chief methods of diminishing the chance of infection in the peritoneum may be divided under four headings: (1) the aseptic method, (2) "vaccination" of the peritoneum, (3) bacteriophage therapy, and (4) chemotherapy.

The first of these, with the exception of one new method, can be omitted from this discussion. The exception is the revived emphasis on air-borne contamination resulting from the work of Hart and Sanger.[65] Although not yet entirely accepted by the surgical world, the employment of ultraviolet irradiation to minimize air-borne contamination has aroused the interest of surgeons everywhere. It is too early to predict that this method will become standard practice.

The idea of producing local peritoneal immunity by introducing killed organisms into the abdominal cavity apparently originated with Dur-

ham[43] and Issaef[25, 72] around 1894. Shortly thereafter Solieri[25, 156] introduced the idea that this immunity was a result of phagocytosis. It is generally believed now that this method calls forth a nonspecific hyperleucocytosis due to which phagocytosis of bacteria rapidly occurs before their toxins are developed and peritonitis becomes established. In the early years (1890 to 1915) Solieri,[156] Miyake,[112] von Mikulicz,[111] and Hirano[70] made contributions to the study of the method. None of these workers indicated its relationship to later adhesion formation. Due to the frequent development of severe body reactions and peritonitis in clinical cases, the method was abandoned by that surgical generation. More recently, Naumann,[120] Hermann,[67] Rankin and Bargen,[138, 139] Steinberg and Goldblatt,[158, 160-162] Dixon and Rixford,[38] and Coller and his associates[23-25, 135] have revived the method. Most of the recent work has involved the employment of either the Rankin-Bargen vaccine or Steinberg's colibactragen. The former has been dropped by most surgeons, including its surgical originator, because of severe clinical reactions and peritonitis.[37, 138] Colibactragen, however, still remains in the field. Its use is not yet accepted as a standard practice in the surgery of the bowel. In view of the recent development of chemotherapy as applied to the problems of the peritoneum, the final acceptance or rejection of colibactragen will probably be delayed. Only two or three of the recent investigators with colibactragen have indicated anything as to its antiadhesion possibilities. Steinberg[159] (1939) stated that in some thousand small animals treated with colibactragen for virulent peritonitis, no adhesions were found. He also remarked that in a few patients, so treated, and observed later at a second laparotomy, no adhesions were encountered. Jones[79] (1939) remarked that he has discontinued the clinical employment of colibactragen because of severe reactions and the frequent development of peritonitis. He doubts that the fibrinopurulent exudate resulting from the use of colibactragen will subside without some adhesion formation, but has no data to this effect. Coller[22] (1940) still sees value in colibactragen but advises using it only in cases with frank peritoneal contamination at operation. He has seen no pathologic harm accrue intraperitoneally from its use in selected cases. Schmidt and co-workers[151] (1941) have reported dog experiments involving the use of colibactragen in the treatment of experimental peritonitis indicating absence of adhesion formation when colibactragen is used twenty-four to forty-eight hours before artificial peritoneal contamination.

Bacteriophage therapy for adhesion prevention is also *sub judice*, the literature[44, 93, 94] indicating that it probably has antibacterial properties in the treatment of coliform and staphylococcal infections in the walled-off spaces of the body where irrigations with large amounts of bacteriophage can be employed. Rixford[149] (1931), Applebaum and MacNeal[3] (1932), Zaytseff-Jern and associates[188] (1932), and Rice[146] (1933) have recently presented communications on the problem. Whatever the merits

of bacteriophage may prove to be in protecting the peritoneum against infection, nothing is known so far of its relationship to the formation of adhesions.

Certainly the most promising of the newer attempts to diminish the chance of infection within the peritoneum is the use of the sulfonamide compounds. There seems little doubt that the danger of peritoneal contamination can be diminished by the local use of these products.[10, 26, 27, 51, 73, 100, 140, 151] However, insufficient data have been reported so far about their relationship to adhesion formation. Work on this phase of the problem is also under way in the author's laboratory.

Limitation of Chemical Peritoneal Injury.—In the era of antiseptic surgery, roughly from 1870 to 1890, there was a high incidence of postoperative adhesion formation following the use of disinfectants and antiseptics within the abdominal cavity. As early as 1891, Delbert, Grandmaison, and Bresset,[35] for instance, had demonstrated that certain chemicals within the peritoneum predispose to adhesion formation. The discontinuance of intraabdominal antisepsis, the increased use of mechanical cleansing and fat solvents for skin preparation in place of strong chemical solutions,[106] and the employment of dry autoclaved gloves have automatically removed much of the hazard of chemical peritoneal damage in the abdominal cavity.

Limitation of Thermal Peritoneal Injury.—Except for two newer developments in operating room procedure, no discussion of thermal injury to the peritoneum is indicated; all surgeons are careful in the use of hot solutions[86] and the actual cautery. In the first place, the possibility of peritoneal damage from ultraviolet irradiation, as used to minimize airborne contamination, must be kept in mind. Hart[64] has the definite impression without statistical proof that peritoneal adhesions are not increased by this exposure. In the second place, the effects on the eye of exposure to brilliant flood lamps for motion-picture photography suggests the warning that surgeons who make motion-picture records of surgical procedures should be careful that damage is not being done to the peritoneum.

Limitation of Peritoneal Injury by Foreign Bodies.—Except for the occasional accidental loss of bulky foreign bodies in the peritoneal cavity and the deliberate employment of material for drainage, the problem of foreign substances in relation to adhesions is limited commonly to two factors. The first, already mentioned (page 124), is the creation of large foreign bodies by tight mass ligature or by extensive deep cauterization, both of which are opposed to good surgical technique. In the second place, the use of certain glove powders has been presented as the cause of peritoneal adhesions. The most seriously offending of these is lycopodium which was popular in a limited way about fifteen years ago and has been largely discarded.[61, 137] Recently, talc has also been accused.[47, 61, 137] Most surgeons believe that ordinary care in cleansing

the external surface of the rubber glove before beginning operation is adequate protection from this danger.

Summary.—The established measures facilitating adhesion prevention by limiting peritoneal injury may be summarized as follows:

1. Scrupulous aseptic technique.
2. Gentle handling of tissues.
3. Accurate, prompt hemostasis with minimal tissue devitalization.
4. Avoidance of intraperitoneal use of chemical solutions.
5. Avoidance of thermal injury by hot solutions, promiscuous charring with the cautery, and unnecessary exposure to ultraviolet and photographic lights.
6. Avoidance of leaving behind in the peritoneal cavity unnecessary foreign bodies, such as long suture ends, unneeded drains, sponges, etc.

II. DIRECT INHIBITION OF FIBROBLASTIC TISSUE PROLIFERATION

Any inhibition of the proliferation of connective tissue must act during the lag period and early phases of tissue repair, as most recently pointed out by Whipple[179, 180] (1940) and before that time by Arey[4] (1936), Harvey and Howes[66] (1930), Carrel[15] (1921), and others. In spite of the fact that very little is known about thus directly inhibiting fibrosis, at least two attempts to prevent adhesion formation from this angle have been recorded. Around 1900 several investigators, including Busch and Bibergeil,[14] Sidorenko,[154] Genino,[55] and Michael,[109] employed a proprietary solution named fibrolysin in the peritoneal cavity for this purpose without demonstrating inhibitory effect on the development of adhesions. We now know that this was an unsuccessful attack on fibrin and not on connective tissue. Somewhat later Hertzler[68, 69] used, and then abandoned, iodides for this purpose on the basis of the traditional belief that iodides permeated all cells of the body, including the connective tissues, and were taken up selectively by damaged and diseased tissues. In recent years it has been shown that iodides are distributed within the body entirely extracellularly except for penetration into red blood cells.[169]

III. METHODS FOR KEEPING APART INJURED PERITONEAL SURFACES UNTIL MESOTHELIALIZATION HAS OCCURRED

Around the beginning of the twentieth century there was a temporary ascendency in medicine of the mechanistic philosophy. This emphasis was reflected in many of the investigations on peritoneal adhesion prevention. To many surgeons the abdominal organs were considered as a collection of pipes, filters, and valves. It is not surprising, then, to find the surgical profession of that period attacking the peritoneal adhesion problem from the mechanical point of view by investigating measures directed toward keeping apart injured or inflamed peritoneal surfaces until mesothelialization had occurred. Most of these measures have been discredited and abandoned (Fig. 2).

Membranes.—Both nonabsorbable and theoretically absorbable substances in the form of sheets or membranes have been employed to separate denuded peritoneal surfaces mechanically.

The results with nonabsorbable materials were uniformly unsuccessful. Commonly tested membranes in both animal and clinical investigations were the foils of silver and other metals,[136, 147, 184] silk and rubber sheets,[182, 184] gold-beater's skin,[113, 182] gutta percha sheets,[147] fresh bladder strips,[184] aristol,[113] "Cargile membrane" (from the peritoneum of the ox[49, 113]) and others. Without present knowledge the failure of these substances could have been predicted. By initiating a foreign body reaction, with attendant exudation and encapsulation, they caused the very process which they were supposed to prevent.

The employment of theoretically absorbable substances like the fetal membranes was proposed years ago and has periodically received experimental attention.[101] The effectiveness of these membranes against peritoneal adhesion formation was not satisfactorily established in earlier years. Recently, the attack has been revived with better results. Johnson[77] (1937) reported successful employment of beef allantoic and human amniotic membrane in the prevention of postoperative adhesions around peripheral nerves and tendons after operative repair, and also tested it in a small number of animals in the peritoneal cavity. When a denuded section of the guinea pig's peritoneum was protected with a patch of allantoic membrane no adhesions formed. The unprotected control areas showed dense adhesions. Johnson advised the use of human amniotic membrane for protection against adhesion formation in the various serous cavities.

Davis and Aries[34] (1937) reported the successful use in dogs of beef allantoic membrane for lessening the amount of adhesions around injured nerves and tendons without sheaths, and on denuded peritoneal surfaces. It was their observation that allantoic membrane is superior to beef and human amniotic membrane for these purposes. In animals, human amniotic membrane devoid of a mucous surface did not prevent intra-abdominal adhesion formation, and beef allantoic membrane prevented adhesions only to the extent of the size of the patch of membrane used.

Chao, Humphreys, and Penfield[18] (1940) used in the meninges sheets of specially prepared human amniotic membrane which they called amnioplastin. After removing the meninges covering areas of the brains of cats, they placed autoclaved sheets of this membrane over the defects. They observed that the membrane acted as a foreign body for a short time but that it was completely absorbed within thirty days. At the end of this period the dural defects had been filled in by a connective tissue layer which was completely separated from the subjacent pia by what appeared to be a continuation of the subdural space. Adhesion formation did not occur when this membrane was employed, but it did occur when other materials were used, such as

fat, metal foils and plates, fascia lata, plain catgut membrane, etc. These workers suggested the use of amnioplastin in the serous spaces without experimental study in these tissues. The histogenetic differences between the meninges and the peritoneum must be kept in mind in appraising this suggestion.

If other animal and clinical investigations confirm in the peritoneum the striking results of these recent studies, a satisfactory method may possibly be anticipated for the surgical handling of large surfaces denuded of peritoneum, but not for the prevention of adhesions elsewhere in the peritoneal cavity.

Lubricants.—In the earliest attempts to prevent adhesions all kinds of mechanical lubricants were tried, such as mineral oil,[29, 121, 134] olive oil,[8, 29, 53] camphorated oil,[134] fat,[71] agar,[53] gum arabic,[167] gelatin,[147, 183] paraffin,[53] vaseline,[29, 182] collodion,[53, 147] and albumin.[184] Just as with nonabsorbable membranes, these lubricants produced foreign body reaction, with increase rather than decrease of adhesions. They have been entirely abandoned.

Production of Increased Fluid in the Abdominal Cavity.—It is possible that injured bowel surfaces might be kept apart by the constant presence of a simple solution in the abdominal cavity long enough to permit mesothelialization. Attempts to immerse the bowel loops are of two types: (1) the introduction of either isotonic or hypotonic solution in large quantities, and (2) the introduction of a smaller amount of hypertonic solution which is expected to produce an adequate transudate for the purpose desired.

The first reports on this antiadhesion measure appeared just before 1900. According to Richardson[147] and Gellhorn,[53] Stern (1899) and Vogel (1902) were the first to undertake animal investigations regarding the merits or demerits of the measure. According to these same references, Muller (1886) and Malcolm (1890) were the first surgeons to test the measure clinically against adhesions. These workers generally used hypertonic saline or glucose solution which, by producing a substantial fibrin-free transudate, created a large amount of fluid between bowel surfaces.

From 1900 to 1925 this general method was tried by several investigators[30, 53, 113, 147] without favorable results except in the case of Buchbinder[12, 13] (Table I). In 1923 Buchbinder reported that in a small number of dog experiments hypertonic glucose largely prevented early fibrinous agglutinations of the bowel. His results were not carried to the terminal stage of adhesion formation. He did not state how he thought the transudate worked, whether by dilution of the exudate coagulation factors, or by mechanical isolation of the intestinal coils. The former opinion was implied.

During the 1930's and through 1940, several animal investigations were reported which dealt with the prevention of peritoneal adhesions

with simple solutions. Ochsner and Garside[124] (1932) presented experiments with normal saline solution in the dog directed against both the formation and re-formation of peritoneal adhesions. One hundred per cent of the control animals formed adhesions as opposed to 85 per cent of the animals given saline solution. In their re-formation studies, the animals given saline solution developed intra-abdominal adhesions in 93 to 100 per cent of cases. In 1934 Rea and Wangensteen[141] reported a small series of rabbit experiments wherein normal saline solution was employed against the formation of peritoneal adhesions. The control group formed such adhesions in 90 per cent of cases, while the experimental animals receiving saline solution formed them in only 63 per cent. In 1939-40 Lehman and Boys[96, 97] employed normal saline solution in a few animals as controls for their work with heparin which will be discussed later. Although their experiments were too few to be conclusive, they suggest no favorable effect. Totten[164] (1940) reported the most favorable experimental study of this kind to date. He employed 20 per cent glucose intra-abdominally in the rabbit against peritoneal adhesion formation and re-formation. A control group of sixteen animals formed adhesions in 100 per cent of cases, as contrasted with 14 per cent in an experimental group of sixteen. In a second experimental study, without controls, 36 per cent of eleven animals re-formed previously divided adhesions.

It is believed that most of the experimental studies reported can be criticized from some angle, the number of experiments, the validity of the controls, the standardization of methods of creating adhesions, the amounts of solution administered, the method of calculating and recording results, or the species of animal employed. Theoretical objections to the method are as follows: (1) All simple crystalloid solutions are rapidly absorbed, and any action must be transient. Hypotonic solutions remain in the peritoneal cavity only a few hours, and hypertonic solutions usually disappear within twenty-four hours.[69, 168] (2) While present the solutions do not remain between the loops of bowel, but tend to gravitate to dependent portions of the abdominal cavity.[53, 183] (3) It is possible that floating of the bowel may actually cause the raw surfaces of the intestines to float into contact.[53] (4) There has never been satisfactory evidence that new growth of mesothelium occurs to any appreciable extent before the fluid is absorbed and the denuded peritoneal surfaces are again in contact.[147] (5) With the use of hypertonic solutions there is always the likelihood of an increase in capillary oozing,[53] and the consequent deposition of fibrin flakes, due to a chemical serosal inflammation. This in itself will tend to create adhesions. Fibrin in considerable quantity may be seen at laparotomy after the administration of fluids intraperitoneally as in operations for hypertrophic pyloric stenosis.[95]

It should be noted that the possible effectiveness of this method might be the result of the dilution of the coagulation factors in the peritoneal

TABLE I

SIMPLE CRYSTALLOID SOLUTIONS (ANIMAL INVESTIGATIONS)

NAME (YR.)	CASES	ANIMALS		PRODUCT USED			TESTED AGAINST	ADHESIONS PRODUCED BY	ADMINISTRATION OF SOLUTION (INTRAPERITONEAL)				INTERVAL BEFORE POST-OPERATIVE EXAMINATION	NO. ANIMALS FORMING OR RE-FORMING ADHESIONS (%)
		SPECIES	NO.	NAME	STRENGTH	VEHICLE			HOW ADMINISTERED	NO. ADMINISTERED	WHEN ADMINISTERED	AMT. ADMINISTERED		
Pope (1914)	Experiment	Rabbits	N.R.* (several)	Saline solution	Normal	–	Adhesion formation	A†	(?) Tube	Single	Close of operation	15 c.c.	7 days	1+
	Experiment	Rabbits	N.R. (several)	Ringer's solution	–	–	Adhesion formation	A	(?) Tube	Single	Close of operation	15 c.c.	7 days	2+
	Controls	Rabbits	N.R. (several)	0	0	0	Adhesion formation	A	0	0	0	0	7 days	2+
Kubota (1922)	Experiment	Rabbits	3	Saline solution	1-3%	–	Adhesion formation	C	(?) Tube	Single	Close of operation	30-100 c.c.	7-21 days	3 (100%)
	Controls	Rabbits	12	0	0	0	Adhesion formation	C	0	0	0	0	1-21 days	12 (100%)
Buchbinder (1927)	Experiment	Dogs	7	Dextrose solution	20%	–	Adhesion formation	C	Needle	Single	Close of operation	N.R.	1-3 days	None‡
	Controls	Dogs	N.R.	0	0	0	Adhesion formation	C	0	0	0	0	1-3 days	(100%)
Ochsner and Garside (1932)	Experiment	Dogs	6	Saline solution	Normal	–	Adhesion formation	C	(?) Tube	Single	Close of operation	Abdomen filled	18 days (average)	6 (100%)
	Experiment	Dogs	13	Saline solution	Normal	–	Adhesion formation	A	(?) Tube	Single	Close of operation	Abdomen filled	18 days	11 (85%)

*N.R. No record.

†A. Scarification of bowel. B. Chemical peritonitis, usually iodine. C. Combination of A and B. D. Donaldson's pledget technique. E. Scratching bowel. F. Perforation of appendix.

‡"None except for occasional fibrin strands."

	Experiment	Dogs	15	Saline solution	Normal	–	Adhesion reformation	C	(?) Tube	Single	Close of operation	Abdomen filled	18 days	14 (93%)
	Controls	Dogs	11	0	0	0	Adhesion reformation	C	0	0	0	0		11 (100%)
Rea and Wangensteen (1934)	Experiment	Rabbits	8	Saline solution	Normal	–	Adhesion formation	C	(?) Tube	Single	Close of operation	20 c.c.	7 days	5 (63%)
	Controls	Rabbits	10	0	0	0	Adhesion formation	C	0	0	0	0	7 days	9 (90%)
Lehman and Boys (1940)	Experiment	Rabbits	8	Saline solution	Normal	–	Adhesion formation	D	Needle	Multiple	Operatively and postoperatively	25 c.c.	7 days	8 (100%)
	Controls	Rabbits	10	0	0	0	Adhesion formation	D	0	0	0	0	7 days	10 (100%)
	Experiment	Dogs	5	Saline solution	Normal	–	Adhesion reformation	F	Needle	Multiple	Operatively and postoperatively	100 c.c.	14 days	5 (100%)
	Controls	Dogs	10	0	0	0	Adhesion reformation	F	0	0	0	0	14 days	10 (100%)
Totten (1940)	Experiment	Rabbits	16	Glucose solution	20%	Normal saline	Adhesion formation	C	(?) Tube	Single	Close of operation	15 c.c. per kg. weight	7-35 days	2 (14%)
	Controls	Rabbits	16	0	0	0	Adhesion formation	C	0	0	0	0	7-35 days	16 (100%)
	Experiment	Rabbits	11	Glucose solution	20%	Normal saline	Adhesion reformation	C	(?) Tube	Single	Close of operation	15 c.c. per kg. weight	7-35 days	4 (36%)
	Controls	None												

exudate rather than of the mechanical separation of damaged peritoneal surfaces. The method will be discussed later from this other point of view.

In summary, the theories behind the attempts to separate loops of bowel by simple solutions are undetermined and at least in part illogical, the clinical reports are of no value, and the results from animal experimentation have been contradictory, inconclusive, and incomplete. However, there are possibilities of value in the method that deserve more adequate study.

Pneumoperitoneum.—Bainbridge[5] (1908) suggested the use of air or oxygen in the abdominal cavity to keep injured peritoneal surfaces apart until healing has occurred. Orndoff[127] (1933) reported the efficacy of oxygen pneumoperitoneum in preventing the re-formation of divided adhesions in some sixty clinical cases as judged by an uneventful postoperative course, and no mortality. No statistical data on actual effectiveness and no experimental work were reported. Pneumoperitoneum has not been reported for the prophylaxis of adhesions by other workers.

Obvious objections to its employment are as follows: (1) The results have never been investigated experimentally and clinical reports are few and not convincing. (2) Hertzler[69] reports that increased intra-abdominal pressure due to air, or its components, lessens peristalsis just as does increased intraluminary pressure in the gastrointestinal tract. If this is true, the apposition of injured bowel surfaces would be made more rather than less likely. (3) Hertzler[69] also states that air exposure lowers the resistance of the peritoneum so that the number of bacteria necessary for production of peritonitis is reduced.

Active and Passive Increase in Movements of Viscera.—Some early workers in the field of the prevention of adhesions assumed that if the injured fibrin-coated bowel surfaces could be kept from maintained contact with each other, by keeping the bowel itself in constant motion until mesothelialization has occurred, fibrous union might be prevented. Active peristalsis was continuously stimulated by various substances, including physostigmin,[167] strychnine,[30] the commoner cathartics,[173] and large soapsuds enemas.[20, 30] Ward[173] states that Malcolm in 1890[103] was the first clinician to test this method. According to Gellhorn,[53] Vogel popularized the method in Germany and Craig in the United States. Although it may be desirable to maintain tonus of the bowel and normally active peristalsis, it would seem undesirable even if possible to maintain a state of active peristalsis with accompanying distress, dehydration, and other potential dangers. The validity of the principle of preventing adhesions by increasing the mobility of the bowel is weakened by the work of Ochsner and Herrmann,[123] who have demonstrated in animals that experimental pericardial adhesions invariably reform in spite of continuous cardiac motion.

Certain passive methods of accomplishing the same effect have been proposed in the past. Abdominal massage after laparotomy as a pro-

phylaxis against adhesion formation has been recommended by occasional surgeons; for example, Cumston[30] (1906) and de Minter[36] (1938). There has never been presented any laboratory or clinical evidence that such massage influences adhesion formation. In the period just preceding the World War a few German workers proposed some bizarre methods, involving passive motion of the viscera, techniques deserving mention only as surgical curiosities. Kroh[90] (1914) and Kirchberg[85] (1914) both proposed a huge suction bell for the entire abdomen by means of which they stated the abdominal contents could be kept in constant motion. Payr[129] administered an iron suspension by mouth and attempted to keep the intestines in motion by moving a large magnet over the abdomen. This extraordinary technique was supported by animal experimentation.

Operative and Postoperative Rearrangements of the Viscera.—The plan of adjusting the relations of the viscera at operation, or postoperatively, is not a modern idea. It was apparently introduced around 1700 by a Parisian surgeon by the name of de la Vanguion.[173] Malcolm[173] is considered the first modern surgeon to practice this method clinically, a measure which still has adherents today. Several different attempts to prevent contact of injured peritoneal surfaces by artificial arrangements or rearrangements of the viscera have been proposed. Such methods include the following: (1) manual replacement of the viscera by the surgeon at the conclusion of the operation;[103, 173] (2) distention of the large bowel immediately after operation with a bulky enema;[53, 54, 147] (3) the use of certain bed positions postoperatively with the idea of separating raw surfaces by gravitation;[20, 83, 142, 147] (4) distending the bladder[178] to prevent the intestines from falling into the cul-de-sac when raw surfaces are left in that region.

In view of the great mobility of the small bowel and omentum, the success of such attempts is hardly likely since it is entirely a result of chance. It is known that following extensive evisceration, the small bowel will return to its normal anatomical position no matter how carelessly it may be replaced. It is, therefore, improbable that any artificial arrangements of the viscera would have any effect in preventing adhesions.

Summary.—Of the various mechanical antiadhesion measures directed toward keeping apart injured peritoneal surfaces until mesothelialization has occurred only two warrant any consideration and neither of them are of accepted value: (1) Of the various membranes proposed, the absorbable amniotic or allantoic membranes may be found to be useful, but before they can be recommended for clinical trial in the abdomen, it is necessary that further animal experimentation be conducted. (2) Suggestive evidence has been produced to the effect that intra-abdominal employment of any simple solution may have some antiadhesion value. Whether this is by virtue of mechanical isolation of bowel loops or from some other mechanism is not yet clear.

IV. REMOVAL OF FIBRIN ALREADY DEPOSITED UPON THE PERITONEAL SURFACES

The rationale of the attack against fibrosis by removing fibrin rests upon the fact that organization can take place only in a pre-existing fibrinous exudate. It is recognized that in a contaminated peritoneum the presence of fibrin is protective through its property of causing temporary adhesions which prevent the spread of infection. This factor is not of prime importance in instances of the division of adhesions when the bowel is not opened. The present section is devoted to attempts which have been made to destroy fibrin after it has been deposited.

The fibrinolytic attack was one of the earliest, being a natural result of incomplete knowledge about the phases and factors of blood coagulation. It dates from 1887 when Weigert reported his specific stain for fibrin.[21, 60] Investigators learned that certain chemical solutions dissolved fibrin in vitro and it was not long before in vivo studies were reported directed toward the prevention of adhesions. One of the practical incentives for the initiation of these fibrinolytic studies was the desire on the part of the surgeons to find something to prevent plugging and encapsulation of drains.[185]

The specific methods employed may be classified as follows: (1) miscellaneous chemical actions, (2) foreign digestive ferments, (3) the stimulation of hyperleucocytosis with resulting phagocytosis and possible autogenous ferment action. In considering these groups, it must be remembered that the various mechanisms are not sharply delimited. In the first two, for instance, the measures are accompanied by hyperleucocytosis.

Chemical Attacks Against Fibrin.—The earliest fibrinolytic substance proposed and tested against peritoneal adhesion formation was "fibrolysin" which the pharmacopoeia describes as liquor thiosinamine with sodium salicylate. According to Sollman[157] this substance was introduced by Hebra and Unna in 1892 and credited by them as effecting absorption of not only fibrin but also scar tissue. During this period Muller[117] is reported to have tested its antiadhesion value experimentally in animals, and Siderenko[117] clinically. Neither described any appreciable therapeutic effect. This substance has long since lost any pretense of efficacy.

Kuhn[88, 89] (1911) noted the fact that hypertonic glucose had fibrinolytic action in vitro and suggested that it might have value if used intraperitoneally to facilitate abdominal drainage. Pope[133] (1914), stimulated by Kuhn's work, conducted mechanical trauma adhesion experiments in animals and reported that hypertonic glucose had no value in their prevention (Table II). Reschke[144, 145] (1921) investigated the effect of hypertonic glucose on peritoneal reabsorption, having in mind its possible use in the treatment of peritonitis. He failed to confirm the fibrinolytic action of hypertonic glucose. Buchbinder[12] (1927), working

TABLE II

HYPERTONIC GLUCOSE (ANIMAL INVESTIGATIONS)

NAME (YR.)	CASES	ANIMALS		PRODUCT USED			TESTED AGAINST	ADHESIONS PRODUCED BY	ADMINISTRATION OF SOLUTION (INTRAPERITONEAL)				INTERVAL BEFORE POST-OPERATIVE EXAMINATION	NO. ANIMALS FORMING OR REFORMING ADHESIONS (%)
		SPECIES	NO.	NAME	STRENGTH	VEHICLE			HOW ADMINISTERED	NO. ADMINISTERED	WHEN ADMINISTERED	AMT. ADMINISTERED		
Pope (1914)	Experiment	Rabbits	N.R.*	Dextrose solution	50%	–	Adhesion formation	A†	N.R.	Single	Close of operation	15 c.c.	7 days	2 +
	Controls	Rabbits	N.R.	0	0	0	Adhesion formation	A	0	0	0	0	7 days	2 +
Buchbinder (1927)	Experiment	Dogs	7	Dextrose solution	20%	0	Adhesion formation	C	Needle	Single	Close of operation	N.R.	1-3 days	None‡
	Controls	Dogs	NR. (a few)	0	0	0	Adhesion formation	C	0	0	0	0	1-3 days	N.R. (100%)
Trusler (1931)	Experiment	Guinea pigs	30	Dextrose solution	50%	–	Adhesion formation	A	N.R.	Single	Close of operation	N.R.	21 days	20 (66%)
	Controls	Guinea pigs	96	Dextrose solution	50%	0	Adhesion formation	A	0	0	0	0	21 days	89 (93%)
	Experiment	Dogs	7	Dextrose solution	50%	–	Adhesion formation	A	N.R.	Single	Close of operation	50 c.c.	42 days	5 (71%)
	Controls	Dogs	15	0	0	0	Adhesion formation	A	0	0	0	0	42 days	15 (100%)
Rea and Wangensteen (1934)	Experiment	Rabbits	7	Glucose solution	10%	–	Adhesion formation	C	N.R.	Single	Close of operation	20 c.c.	7 days	2 (29%)
	Controls	Rabbits	10	0	0	0	Adhesion formation	C	0	0	0	0	7 days	9 (90%)

*N.R. No record.

†A. Scarification of bowel. B. Chemical peritonitis, usually iodine. C. Combination of A and B. D. Donaldson's pledget technique. E. Scratching bowel. F. Perforation of appendix.

‡"Occasional thin strands of fibrin."

with dogs, employed hypertonic dextrose solution to prevent the encapsulation and plugging of abdominal drains and reported that the formation of adhesions between the loops around the drainage material was diminished (Table II). He presumably related this effect to dilution of the exudate rather than to fibrinolytic action. David and Sparks[33] (1928) presented experimental evidence to the effect that following the intraperitoneal introduction of hypertonic glucose solution, plastic exudate is diminished and bacteria present are permitted to pass more readily than normal from the peritoneal cavity into the lymphatic and blood streams. Attendant dangers noted were dehydration and distention. Trusler[166] (1931), working with guinea pigs, found that when 50 per cent dextrose was used, adhesions formed in 66 per cent of experimental animals as against 93 per cent of controls. With dogs, also employing 50 per cent dextrose, the experimental animals formed adhesions in 71 per cent as against 100 per cent in the controls. Rea and Wangensteen[141] (1934), in a small group of rabbit investigations, found that when 10 per cent glucose was employed only 29 per cent of animals formed adhesions. In the control group the rate of adhesion formation was 90 per cent.

In summary, experimental studies have not demonstrated uniformly a satisfactory fibrinolytic action of hypertonic glucose. As practical antiadhesion measures fibrinolytic attacks with hypertonic glucose and other such substances have been discarded.

Foreign Digestive Ferments.—The earliest investigations with ferments dealt with pepsin and trypsin, both of which were soon abandoned as antiadhesion measures. The solutions were too unstable for practical use, even when freshly made before operation.[75, 87, 124, 131, 132, 170, 171, 184] In high concentrations, and even in concentrations necessary for surgical or clinical effectiveness, they commonly produced a marked peritonitis. Both ferments were found to be neutralized by the antitrypsin normally found in peritoneal transudates and exudates.

A widely popularized attack on adhesions from the fibrinolytic angle is the employment of a foreign ferment; namely, papain.

Experimental (Table III).—Kubota[87] (1922), having confirmed the unsatisfactory results with pepsin and trypsin, tested experimentally in rabbits the value of papain, a vegetable digestive ferment obtained from the unripe fruit of the pawpaw tree. Working with rabbits he administered a single dose of papain in solution at the close of operation for the production of adhesions, but failed to mention the amount given or the solution used for the vehicle. It was found that 100 per cent of the controls formed peritoneal adhesions, while only 63 per cent of the experimental animals formed them. Ochsner and Mason[122] (1928) reported a substantial series of experiments with papain solution. They administered a single dose at the close of an operation designed to create adhesions. Though they stated that papain was effective in preventing

the formation of adhesions, their report failed to note the number of control animals, the amount of papain administered, the vehicle used, and the number of animals examined at the end of the experiments. Trusler[166] (1931) reported a large series of experiments in guinea pigs, and a small series in dogs. His evidence suggested slight, if any, effectiveness of papain against adhesion formation. In 1932 Ochsner and Garside[124] reported another substantial series of papain experiments in which both dogs and rabbits were used. The papain was administered in large amounts of saline solution at the close of an operation to create or divide adhesions. In the dog experiments testing adhesion formation, only 34 per cent of adhesions reformed; no controls for these experiments were reported. In the rabbit experiments testing adhesion formation, only 38 per cent of the animals formed adhesions; again there were no controls. Rea and Wangensteen[141] (1934) reported a small series of rabbit experiments testing the value of a single dose of papain solution against adhesion formation and found that only 11 per cent of the experimental animals formed them as compared with 90 per cent in the controls. They failed to mention the vehicle used and the total quantity of fluid given intraperitoneally at operation. Fausel[46] (1934) reported a small series of animal experiments with papain but did not mention the species employed. He filled the abdominal cavity with papain solution at the close of an adhesion-forming operation and examined them fifteen days later. The control animals showed a "3 plus" formation of adhesions, while the papain animals presented a "1 plus" formation. A few animals were observed for the value of papain against the reformation of adhesions, the figure obtained being again "1 plus." Bogart[9] (1937) reported several small series of papain experiments in rabbits. In one group of six experimental animals papain was administered in sodium citrate solution after adhesion creating operations, and it was observed that only two (33 per cent) of the animals formed adhesions. In a similar experimental group of only three rabbits in which water was the vehicle for the papain, all of the animals formed adhesions. Four uncontrolled experiments with papain in the prevention of the reformation of adhesions were tried in which sodium citrate was again the vehicle. Two of these animals (50 per cent) reformed adhesions. In all of these experiments Bogart failed to record the amounts of papain solution injected after the respective operations. Donaldson[40] (1938) reported a small series of rabbit experiments with adequate details; he failed to find papain effective in the prevention of the formation of peritoneal adhesions. However, he did not record reformation experiments, and no control group was recorded for the studies on formation. Lehman and Boys[97] (1940) reported a small series of papain experiments in dogs which were conducted only for the purpose of comparative studies for other experiments. Papain was not found effective in our hands to prevent reformation of divided adhesions.

TABLE III

PAPAIN (ANIMAL INVESTIGATIONS)

NAME (YR.)	CASES	ANIMALS		PRODUCT USED			TESTED AGAINST	ADHESIONS PRODUCED BY*	ADMINISTRATION OF SOLUTION (INTRAPERITONEAL)				INTERVAL BEFORE POST-OPERATIVE EXAMINATION	NO. ANIMALS FORMING OR REFORMING ADHESIONS (%)
		SPECIES	NO.	NAME	STRENGTH	VEHICLE			HOW ADMINISTERED†	NO. ADMINISTERED	WHEN ADMINISTERED	AMT. ADMINISTERED		
Kubota (1922)	Experiment	Rabbits	22	Kaktol	N. R.†	N.R.	Adhesion formation	C	N.R.	Single	Close of operation	N.R.	7-28 days	14 (64%)
	Controls	Rabbits	12	0	0	0	Adhesion formation	C	0	0	0	0	7-28 days	12 (100%)
Ochsner and Mason (1928)	Experiment	Rabbits	39	Parke, Davis & Co.	1:1,000 1:40,000	N.R.	Adhesion formation	C	N.R.	Single	Close of operation	N.R.	4-49 days	"None to few adhesions"
	Controls	Rabbits	N.R.	0	0	0	Adhesion formation	C	0	0	0	0	4-49 days	"Many adhesions"
	Experiment	Dogs	8	Parke, Davis & Co.	1:1,000 1:40,000	N.R.	Adhesion reformation	C	N.R.	Single	Close of operation	N.R.	14-49 days	8 (100%)
	Controls	Dogs	8	0	0	0	Adhesion reformation	C	0	0	0	0	14-49 days	3 (38%)
Trusler (1931)	Experiment	Guinea pigs	24	Parke, Davis & Co.	1:5	N.R.	Adhesion formation	A	N.R.	Single	Close of operation	4-10 c.c.	21 days	20 (83%)

*A. Scarification of bowel. B. Chemical peritonitis, usually iodine. C. Combination of A and B. D. Donaldson's pledget technique. E. Scratching bowel. F. Perforation of appendix.

†N.R. No record.

	Controls	Guinea pigs	96	0	0	0	Adhesion formation	A	0	0	0	0	21 days	89 (93%)
	Experiment	Dogs	4	Parke, Davis & Co.	1:40,000	N.R.	Adhesion formation	A	N.R.	Single	Close of operation	50 c.c.	42 days	4 (100%)
	Controls	Dogs	15	0	0	0	Adhesion formation	A	0	0	0	0	42 days	15 (100%)
Ochsner and Garside (1932)	Experiment	Dogs	44	Parke, Davis & Co.	1:50,000	Saline solution	Adhesion reformation	C	N.R.	Single	Close of operation	Abdomen filled	18 days	15 (34%)
	Controls	Dogs	11	0	0	0	Adhesion formation	C	0	0	0	0	18 days	11 (100%)
	Experiment	Rabbits	16	Parke, Davis & Co.	1:50,000	Saline solution	Adhesion formation	C	N.R.	Single	Close of operation	N.R.	18 days	6 (38%)
	Controls	None												
Rea and Wangensteen (1934)	Experiment	Rabbits	17	Parke, Davis & Co.	1:50,000	N.R.	Adhesion formation	C	N.R.	Single	Close of operation	20 c.c.	7 days	2 (12%)
	Controls	Rabbits	10	0	0	0	Adhesion formation	C	0	0	0	0	7 days	9 (90%)
Fausel (1934)	Experiment	N.R.	7	Parke, Davis & Co.	1:1,000	Saline solution	Adhesion formation	C	N.R.	Single	Close of operation	Abdomen filled	3-15 days	1 +
	Controls	N.R.	7	0	0	0	Adhesion formation	C	0	0	0	0	3-15 days	3 +
	Experiment	N.R.	8	Parke, Davis & Co.	1:1,000	Saline solution	Adhesion reformation	C	N.R.	Single	Close of operation	Abdomen filled	5-11 days	3 +

TABLE III—CONT'D

NAME (YR.)	CASES	ANIMALS		PRODUCT USED			TESTED AGAINST	ADHESIONS PRODUCED BY*	ADMINISTRATION OF SOLUTION (INTRAPERITONEAL)				INTERVAL BEFORE POST-OPERATIVE EXAMINATION	NO. ANIMALS FORMING OR REFORMING ADHESIONS (%)
		SPECIES	NO.	NAME	STRENGTH	VEHICLE			HOW ADMINISTERED†	NO. ADMINISTERED	WHEN ADMINISTERED	AMT. ADMINISTERED		
	Controls	None												
	Experiment	N.R.	3	Parke, Davis & Co.	1:1,000	Saline solution	Adhesion formation	Gastric and gall bladder operations	N.R.	Single	Close of operation	Abdomen filled	5-42 days	None to 1+
	Controls	N.R.	3	0	0	0	Adhesion formation	Gastric and gall bladder operations	0	0	0	0	5-42 days	3+
Bogart (1937)	Experiment	Rabbits	6	Parke, Davis & Co.	1:25,000	Sodium citrate	Adhesion formation	C	N.R.	Single	Close of operation	N.R.	10-60 days	2 (33%)
	Controls	None												

	Experiment	Rabbits	3	Parke, Davis & Co.	1:25,000	Water	Adhesion formation	C	N.R.	Single	Close of operation	N.R.	12 days	3 (100%)
	Experiment	Rabbits	4	Parke, Davis & Co.	1:25,000	Sodium citrate	Adhesion re-formation	C	N.R.	Single	Close of operation	N.R.	21 days	2 (50%)
	Controls	None												
Donaldson (1938)	Experiment	Rabbits	11	Parke, Davis & Co.	1:50,000 (fresh)	Hartman's solution	Adhesion formation	D	N.R.	Single	Close of operation	Abdomen filled	30 days (aver.)	11 (100%)
	Experiment	Rabbits	5	Parke, Davis & Co.	1:50,000 (1 day old)	Hartman's solution	Adhesion formation	D	N.R.	Single	Close of operation	Abdomen filled	30 days	5 (100%)
	Controls	None												
	Experiment	None					Adhesion re-formation							
	Controls	Rabbits	10	0	0	0	Adhesion re-formation	D	0	0	0	0	30 days	10 (100%)
Lehman and Boys (1940)	Experiment	Dogs	5	Parke, Davis & Co.	1:20,000	Hartman's solution	Adhesion re-formation	F	Needle	Multiple	Close of operation and post-operatively	100 c.c.	14 days	5 (100%)
	Controls	Dogs	10	0	0	0	Adhesion re-formation	F	0	0	0	0	14 days	10 (100%)

A careful review of the experimental reports indicates several general criticisms that can be levelled against the methods employed, including (1) the varying and impressionistic methods of calculating and recording results, (2) the variety and unreliability of the means of producing adhesions, and (3) the vehicle employed to introduce the ferment.

Most observers have reported the number of animals that show adhesions rather than the number of adhesions formed. Ochsner and his associates summarize their results by such statements as "slight or no adhesions," or "either no adhesions or a few fine veil-like adhesions," etc. Fausel described his results in "plus" amounts of varying number. Recognizing that the fundamental conditions of the problem make any numerical method necessarily inaccurate, Lehman and I attempted to obtain a more objective result by an actual count of the formed or reformed adhesions. In recent work[98] the count has been supplemented by measurement of the actual widths of the adhesions.

Donaldson[40, 41] has pointed out that many experimental results are also open to criticism because the common methods of scarification do not necessarily result in adhesion formation in 100 per cent of control animals. He developed in rabbits a special method, including the introduction of a foreign body, for producing adhesions. Ochsner and Garside[124] subjected 186 dogs to small bowel scarification and iodine application, and in 11 of them (3.4 per cent) failed to obtain adhesion formation. Elliott and Meleney[45] obtained adhesions in their control studies with the scarification method in only 87 per cent, Rea and Wangensteen[141] in only 90 per cent of their animals. Lehman and I[96, 97, 99] have found in dogs that any one of various experimental methods results in a greatly differing extent of adhesion formation in individual animals. The range varies from none to twenty-five or more separate adhesions. We have found further that the effectiveness of any method employed to prevent reformation can be properly estimated only in those animals that present more than a minimum number of adhesions (five to ten). In order to evaluate accurately the results of experimental studies, the extent of adhesions should be recorded and only animals with a substantial number of adhesions should be subjected to experimental study.

Finally, the use of another antiadhesion substance as a vehicle for the ferment is open to criticism. The employment by Bogart of sodium citrate as a vehicle for the introduction of papain prevents the evaluation of the effectiveness of papain alone.

Clinical (Table IV).—The first American clinical study reported is that of Ochsner and Storck in 1936.[126] As judged by the smoothness of the postoperative course papain was considered a useful method of therapy. Thirty-seven of 213 laparotomies came to reoperation, and of these 15 (40 per cent) showed adhesion formation or reformation. Four cases died. In 1 of 2 cases studied post mortem, adhesions were present.

TABLE IV

PAPAIN (CLINICAL INVESTIGATIONS)

NAME (YR.)	PRODUCT USED	TESTED AGAINST	CASES	FIRST OPERATION				ADHESION CHECK AT REOPERATION		ADHESION CHECK AT POST MORTEM		
				TYPE OPERATIONS	NO. CASES	NO. CASES WITH ADHESIONS (%)	HOW PRODUCT USED	NO. CASES	NO. CASES WITH ADHESIONS (%)	NO. DEATHS	NO. POST-MORTEM EXAMINATIONS	NO. CASES WITH ADHESIONS (%)
Ochsner and Storck (1936)	Parke, Davis & Co. 1:20,000	Adhesion re-formation 89%, adhesion formation 11%	Experiment	Major abdominal and obstetric operations	231	132 (40%)	1,000 c.c. at close of operation	37	15 (40%)	4	2	1 (50%)
			Controls	(None)								
Bogart (1937)	Parke, Davis & Co. 1:25,000	Adhesion re-formation	Experiment	Operations for intestinal obstruction	30	30 (100%)	1,500 c.c. at close of operation	0	0	2	2	1 (50%)
			Controls	(None)								
Elliott and Meleney (1937)	Parke, Davis & Co. 1:20,000	Adhesion re-formation	Experiment	Operation for abdominal adhesions	34	34 (100%)	500 c.c. at close of operation	4	4 (100%)*	N.R.†	N.R.	–
			Controls	Operation for abdominal adhesions	38	38 (100%)	0	2	2 (100%)*	N.R.	N.R.	–
Mullen (1938)	Parke, Davis & Co. 1:20,000	Adhesion re-formation	Experiment	Operation for abdominal adhesions	5	5 (100%)	1,000 c.c. at close of operation	1 (op.) 1 (P)‡	2 (40%)	1	0	–
			Controls	(None)								

*Investigator could not tell if some of these adhesions had been left undivided at first operation.
†*N.R.* No record.
‡*P* Peritoneoscope.

There was no control group. The chief value of this large series of cases lies in the demonstration that papain solution is safe for clinical employment.

Bogart[9] (1937) reported three small uncontrolled series of clinical cases in which papain was employed against adhesion formation. In each of these he used a different vehicle. None of the cases came to re-operation. One patient who died, and was subjected to post-mortem examination, presented adhesions.

Elliott and Meleney[45] (1937) presented the only well-controlled series of cases of papain administration. They compared with the papain group a series of control cases of the same distribution as to age, sex, diagnosis, and operative procedures. They noted a satisfactory post-operative course in 87 per cent of the 34 papain cases as against 77 per cent in 38 control cases. This fact, however, can only be considered as referring to the safety of the measure. As no cases came to relaparotomy or to post-mortem study, no conclusions can be drawn as to its actual effectiveness.

The series of 5 clinical cases reported by Mullen[116] (1938) is too small in number to permit conclusions.

In summary, the experimental work on papain is inconclusive and the results are in part contradictory. The clinical reports offer no accept able evidence for or against its effectiveness. Regardless of the possible effectiveness of papain, there are certain generally accepted difficulties attending its use in the peritoneal cavity. In the first place, the only available American preparation of papain is slightly unstable and must be freshly made up before each operation. In addition, as pointed out by Garside,[52] it has been found difficult to manufacture a sterile papain powder which will retain its ferment potency. In the second place, concentrations high enough for effectiveness frequently produce a chemical peritonitis. Finally, like trypsin, papain has no value in the presence of transudate or exudate because it is also neutralized by the antitrypsin normally present.[52, 126] For these reasons, and because of its probably unproved value, the popularity of papain is apparently diminishing.

Stimulation of Intraperitoneal Leucocytosis.—Up to around 1925 an occasional surgeon or investigator, as for example Graser in 1894,[60] noted and reported that fibrin did not form in the presence of pus, but it was not until fifteen years ago that this observation was correlated with adhesion formation and made use of in adhesion prophylaxis. Naumann[120] (1925) suggested the digestion of fibrin by leucocytic ferments when experimenting with the so-called peritoneal vaccines. He based his proposal on the observation that a peritonitis with abundant exudate frequently heals without adhesions, and that in this recovery the leucocytes play the effective role. Naumann experimentally produced sterile abscesses in the dog by injecting turpentine oil in saline solution into the properitoneal connective tissue. By this method he claimed to have

stimulated an excessive intraperitoneal production of leucoproteoses with resulting proteolytic digestion of fibrin.

Simple solutions of crystalloids and the "peritoneal vaccines" both have been previously discussed, the former from the point of view of mechanical separation of inflamed surfaces, and the latter from the point of view of minimizing damage from infection. If either of these has an effect in diminishing adhesions, it must be remembered that the stimulation of leucocytosis in the peritoneum also results from their intraperitoneal administration.

The only deliberate attempt to employ the mechanism of hyperleucocytosis for fibrin removal is that involving the use of amniotic fluid concentrate. When this substance was first proposed, the rationale of its action was based on the absence of adhesions between the amniotic sac and the fetus. This first hint that amniotic fluid might be effective came from a clinical impression that Caesarean section was followed by a lower incidence of peritoneal adhesions than other pelvic laparotomies. Shortly thereafter, its effectiveness was ascribed to leucocytic action. The rationale of the employment of amniotic fluid now accepted is that it produces a protective layer of fibrin on serous surfaces and a moderate leucocytosis which is followed later by a complete resolution of the fibrinous deposit.[75, 76] Johnson and co-workers[78] (1936) feel that of all the activators of peritoneal hyperleucocytosis, amniotic fluid concentrate is the most innocuous and effective, producing abundant leucocytosis but without overstepping the physiologic threshold of peritoneal irritation.

Experimental (Table V).—Johnson[75] (1927) presented a small series of experiments on guinea pigs with negative results. Warren[174] (1928) reported a large series of similar guinea pig experiments, and observed that adhesions formed in only 48 per cent of the animals receiving amniotic fluid as compared with 100 per cent of the controls. Lacey[91] (1930) reported several small series of amniotic fluid experiments with rats. He used a scarification technique for producing adhesions that was effective in all control cases. He did not find amniotic fluid effective in preventing adhesions. In a small dog series, the results were essentially the same. Trusler[166] (1931) reported a substantial number of both dog and guinea pig experiments. In the control dogs his adhesion-producing technique was 100 per cent effective and in the control guinea pigs 93 per cent effective. Approximately 75 per cent of both groups of animals receiving amniotic fluid formed adhesions. Yardumian and Cooper[184] (1934) reported a large series of uncontrolled rat experiments with amniotic fluid in which 100 per cent formed peritoneal adhesions. Rea and Wangensteen[141] (1934) tested its value in rabbits, using a combined technique of chemical and mechanical trauma. The results were striking. Ninety per cent of the control animals formed adhesions; whereas, only 23 per cent of the experimental animals formed adhesions. Gepfert[56] (1936) presented the results of a few dog experiments (number not given) and found that adhesions formed in all animals. He remarked

TABLE V

AMNIOTIC FLUID CONCENTRATE (ANIMAL INVESTIGATIONS)

NAME (YR.)	CASES	ANIMALS		PRODUCT USED			TESTED AGAINST	ADHESIONS PRODUCED BY*	ADMINISTRATION OF SOLUTION (INTRAPERITONEAL)				INTERVAL BEFORE POST-OPERATIVE EXAMINATION	NO. ANIMALS FORMING OR REFORMING ADHESIONS %
		SPECIES	NO.	NAME	STRENGTH	VEHICLE			HOW ADMINISTERED	NO. ADMINISTERED	WHEN ADMINISTERED	AMT. ADMINISTERED		
Johnson (1927)	Experiment	Guinea pigs	5	Hospital prepared	(Boiled)	–	Adhesion formation	(A)	N.R.†	Single	Close of operation	15 c.c.	6-20 days	5 (100%)
	Experiment	Guinea pigs	5	Hospital prepared	(Unboiled)	–	Adhesion formation	(A)	N.R.	Single	Close of operation	15 c.c.	6-20 days	1 (20%)
	Controls	Guinea pigs	4	0	0	0	Adhesion formation	(A)	0	0	0	0	10 days	4 (100%)
Warren (1928)	Experiment	Guinea pigs	80	Amfetin (Lilly)	–	–	Adhesion formation	(A)	N.R.	Single	Close of operation	10 c.c.	N.R.	38 (48%)
	Controls	Guinea pigs	21	0	0	0	Adhesion formation	(A)	0	0	0	0	N.R.	21 (100%)
	Experiment	Guinea pigs	8	Amfetin (Lilly)	–	–	Adhesion formation	(B)	N.R.	Single	Close of operation	10 c.c.	N.R.	2 (25%)
	Controls	Guinea pigs	6	0	0	0	Adhesion formation	(B)	0	0	0	0	N.R.	6 (100%)
Lacey (1930)	Experiment	Rats	8	Amfetin (Lilly)	–	–	Adhesion formation	(A) Minimum	N.R.	Single	Close of operation	5 c.c.	48 days	8 (100%)
	Controls	Rats	3	0	0	0	Adhesion formation	(A) Minimum	0	0	0	0	48 days	3 (100%)

*A. Scarification of bowel. B. Chemical peritonitis, usually iodine. C. Combination of A and B. D. Donaldson's pledget technique. E. Scratching bowel. F. Perforation of appendix.

†N.R. No record.

	Experiment	Rats	3	Amfetin (Lilly)	–	–	Adhesion formation	(A) Maximum	N.R.	Single	Close of operation	5 c.c.	14-21 days	2 (67%)
	Controls	Rats	3	0	0	0	Adhesion formation	(A) Maximum	0	0	0	0	14-21 days	3 (100%)
	Experiment	Rats	3	Amfetin (Lilly)	–	–	Adhesion formation	(A) Minimum	N.R.	Single	Close of operation	5 c.c.	7-14 days	3 (100%)
	Controls	Rats	3	0	0	0	Adhesion formation	(A) Minimum	0	0	0	0	7-14 days	3 (100%)
	Experiment	Rats	4	Amfetin (Lilly)	–	–	Adhesion formation	(B)	N.R.	Single	Close of operation	5 c.c.	1-5 days	4 (100%)
	Controls	Rats	2	0	0	0	Adhesion formation	(B)	0	0	0	0	1-5 days	2 (100%)
	Experiment	Dogs	5	Amfetin (Lilly)	–	–	Adhesion formation	Enterostomies	N.R.	Single	Close of operation	25 c.c.	42-56 days	4 (80%)
	Controls	Dogs	2	0	0	0	Adhesion formation	Enterostomies	0	0	0	0	42-56 days	2 (100%)
Trusler (1931)	Experiment	Dogs	21	Amfetin (Lilly)	–	–	Adhesion formation	(A)	N.R.	Single	Close of operation	50 c.c.	42 days	16 (76%)
	Controls	Dogs	15	0	0	0	Adhesion formation	(A)	0	0	0	0	42 days	15 (100%)
	Experiment	Guinea pigs	353	Amfetin (Lilly)	–	–	Adhesion formation	(A)	N.R.	Single	Close of operation	N.R.	21 days	261 (74%)
	Controls	Guinea pigs	96	0	0	0	Adhesion formation	(A)	0	0	0	0	21 days	89 (93%)

TABLE V—CONT'D

NAME (YR.)	CASES	ANIMALS		PRODUCT USED			TESTED AGAINST	ADHESIONS PRODUCED BY*	ADMINISTRATION OF SOLUTION (INTRAPERITONEAL)				INTERVAL BEFORE POST-OPERATIVE EXAMINATION	NO. ANIMALS FORMING OR REFORMING ADHESIONS %
		SPECIES	NO.	NAME	STRENGTH	VEHICLE			HOW ADMINISTERED	NO. ADMINISTERED	WHEN ADMINISTERED	AMT. ADMINISTERED		
Yardumian and Cooper (1934)	Experiment	Rats	74	Amfetin (Lilly)	–	–	Adhesion formation	(A)	N.R.	Single	Close of operation	N.R.	N.R.	74 (100%)
	Controls	Rats	18	0	0	0	Adhesion formation	(A)	0	0	0	0	N.R.	14 (78%)
Rea and Wangensteen (1934)	Experiment	Rabbits	18	Amfetin (Lilly)	–	–	Adhesion formation	(C)	N.R.	Single	Close of operation	20 c.c.	7 days	4 (23%)
	Controls	Rabbits	10	0	0	0	Adhesion formation	(C)	0	0	0	0	7 days	9 (90%)
Gepfert (1936)	Experiment	Dogs	"Small series"	Amfetin (Lilly)	–	–	Adhesion formation	(C)	N.R.	Single	Close of operation	100 c.c.	21 days	N.R. (100%)‡
	Controls	(None)												
Lehman and Boys (1940)	Experiment	Rabbits	8	Amfetin (Lilly)	–	–	Adhesion formation	(D)	Needle	Multiple	Close of operation and post-operatively	25 c.c.	14 days	8 (100%)
	Controls	Rabbits	10	0	–	–	Adhesion formation	(D)	0	0	0	0	14 days	10 (100%)
	Experiment	Dogs	5	Amfetin (Lilly)	–	–	Adhesion re-formation	(F)	Needle	Multiple	Close of operation and post-operatively	100 c.c.	14 days	5 (100%)
	Controls	Dogs	10	0	0	0	Adhesion re-formation	(F)	0	0	0	0	14 days	10 (100%)

‡"Almost as many as in controls, but less dense."

that the adhesions were "almost as many as in the controls, but were less dense and easier to separate." Lehman and Boys[96, 97, 99] (1940) reported a few amniotic fluid experiments in dogs and rabbits as a comparative series for other adhesion studies. The results in the rabbit indicated no effective action of amniotic fluid in the prevention of the initial formation of adhesions. Most experimental studies on amniotic fluid have dealt with this phase rather than with the prevention of the re-formation of adhesions following their division. The extremely small series of Lehman and Boys in dogs is the only one dealing with the latter problem. The adhesions found in these animals were more extensive than those found after any other substance used.

In general, the same criticisms can be directed toward the reported experiments with amniotic fluid that have been pointed out in discussing the experiments with papain. In addition, the results are diametrically contradictory as between various experimental reports. It cannot be said that amniotic fluid has been proved effective in preventing adhesions from the experimental angle.

Clinical (Table VI).—Johnson[75] (1927) in 35 Caesarean sections filled the abdominal cavity with amniotic fluid at the close of operation. The postoperative courses were satisfactory. Eighteen of the cases came to relaparotomy, and in 3 of them (17 per cent) adhesions were encountered. In 1928[76] he submitted another report of two groups of cases, one a series of 41 Caesarean sections, the other a series of 30 major gynecologic laparotomies. None of the gynecologic cases came to relaparotomy or to death. In the Caesarean section cases, 24 came to subsequent laparotomy, and of them 7 (30 per cent) showed adhesion formation. Johnson gave no control figures on the incidence of adhesions following Caesarean section at his hands. Young and Marks[186] (1934) reported 49 cases of operation on the large bowel with 46 controls. None of the control series came to relaparotomy, and in 8 cases coming to postmortem examination, no record was made of the presence or absence of peritoneal adhesions. In the amniotic fluid group 3 patients came to autopsy, but no mention of adhesions was found in the published report. None of these patients came to relaparotomy. Gepfert[56] (1936) and Gepfert and Stone[57] (1939) supplemented Gepfert's preliminary animal studies with clinical reports, but could give no actual demonstration of the antiadhesion effectiveness of amniotic fluid since none of the cases died or came to relaparotomy.

In summary, the theoretical basis for the use of amniotic fluid is indefinite and confused. The experimental work reported is unconvincing because it is so largely contradictory. Finally, the clinical reports present no evidence of effectiveness in preventing adhesions, although they demonstrate that the intraperitoneal use of this substance is clinically safe. The unsatisfactory status of amniotic fluid in relation to the problem of adhesions is reflected in its diminishing popularity.

TABLE VI

AMNIOTIC FLUID CONCENTRATE (CLINICAL INVESTIGATIONS)

NAME (YR.)	PRODUCT USED	TESTED AGAINST	CASES	FIRST OPERATION				ADHESION CHECK AT REOPERATION		ADHESION CHECK AT POST MORTEM		NO. CASES WITH ADHESIONS (%)
				TYPE OPERATIONS	NO. CASES	NO. CASES WITH ADHESIONS (%)	HOW PRODUCT USED	NO. CASES	NO. CASES WITH ADHESIONS (%)	NO. DEATHS	NO. POST-MORTEM EXAMINATIONS	
Johnson (1927)	Hospital prepared	Adhesion formation	Experiment	Caesarean sections	35	2 (6%)	Abdomen filled at close of operation (R.D.I.*)	18	3 (17%)	0	--	--
			Controls	(None)								
Johnson (1928)	Amfetin (Lilly)	Adhesion formation	Experiment	Caesarean sections	41	2 (5%)	50 c.c. at close of operation (R.D.I.)	24	7 (30%)	0	--	--
			Experiment	Major surgical and gynecologic operations	30	7 (23%)	25-50 c.c. at close of operation (R.D.I.)	0	--	0	--	--
			Controls	(None)								

*R.D.I. Record difficult (to) interpret.
†N.R. No record.

Kimpton (1932)	Amfetin (Lilly)	Adhesion formation	Experiment	Intestinal adhesions	1	1 (100%)	500 c.c. at close of operation	0	--	0	--	--
			Controls	Intestinal adhesions	1	1 (100%)	0	1	1 (100%)	0	--	--
Young and Marks (1934)	Amfetin (Lilly)	Adhesion formation	Experiment	Large bowel surgery	49	N.R.†	50-200 c.c. 8 hr. pre-operatively (R.D.I.)	0	--	3	3	N.R. regarding adhesions
			Controls	Large bowel surgery	46	N.R.	0	0	--	8	N.R.	N.R.
Gepfert (1936)	Amfetin (Lilly)	Adhesion formation	Experiment	Major gynecologic operations	50	44 (88%)	200-400 c.c. at close of operation	0	--	3	1	"Numerous filmy adhesions"
			Controls	Major gynecologic operations	50	18 (36%)	0	0	--	0	--	--
Gepfert and Stone (1939)	Amfetin (Lilly)	Adhesion formation	Experiment	Major gynecologic operations	102	N.R. (54%)	400 c.c. at close of operation	0	--	0	--	--
			Controls	Major gynecologic operations	125	N.R. (40%)	0	0	--	0	--	--

Summary.—Although there is some logic in the principle, animal investigations and clinical reports suggest that no fibrinolytic agent has been found effective in adhesion prevention. It should particularly be noted that a critical appraisal of the evidence dealing with papain, at present perhaps the most popular substance for adhesion prevention, indicates that its supposed effectiveness is actually unproved both experimentally and clinically.

V. PREVENTION OF THE COAGULATION OF THE PERITONEAL EXUDATE

Between the time of the production of a peritoneal exudate and its subsequent coagulation with the deposition of fibrin on injured serosal surfaces, there is a short interval of time which Hertzler[9, 69] has estimated at anywhere from ten minutes to two hours, the time varying with the type and severity of the peritoneal insult. On the assumption that a serous peritoneal exudate coagulates by the same mechanism as the blood plasma, measures used during this period of time have been employed to neutralize some one plasma coagulation factor and thus presumably to prevent the formation of fibrin. The rationale of the anticoagulant attack against adhesion formation has already been pointed out (page 123); namely, that in the absence of fibrin, organization cannot occur.

Although Lehman and Boys[97] have presented incomplete evidence that the attempted prevention of fibrin formation in the presence of peritoneal contamination may not be as disastrous as might be expected, the warning already noted must be kept in mind; namely, that by present knowledge the employment of any such method must for safety be limited to the clean peritoneum.

The past two decades have seen advances in the fundamental knowledge of the nature and significance of certain of the coagulation factors, especially calcium, prothrombin, and thrombin. Since these data cannot be summarized here, it is sufficient to say that the phenomenon of coagulation involves two consecutive reactions: the first is the interaction between prothrombin, calcium, and thrombokinase; the second, the reaction of fibrinogen with thrombin to form fibrin.

Attempts to interfere with the coagulation mechanism have been directed against all of the available factors in the above reactions, and include the following substances: oxalates and citrates to neutralize calcium; peptone supposedly to neutralize fibrinogen; hiruden to neutralize thrombokinase; and, recently, heparin to neutralize thrombin and possibly prothrombin and thrombokinase. Finally, dilution of the peritoneal exudate to the point of ineffectiveness of all factors of coagulation has been proposed by the intraperitoneal administration of a large amount of a simple crystalloid solution.

Dilution of All Coagulation Factors.—The use of large quantities of simple crystalloid solutions in preventing adhesions has already been discussed from three points of view; namely, (1) mechanical separation

of injured surfaces; (2) floating the bowel into new or normal positions; (3) the stimulation of intraperitoneal leucocytosis. A few authors[12, 13, 177] have suggested that possible effects of such use of these solutions have been the result of the dilution of the coagulation factors of the peritoneal exudate. Marvel [104] (1907) pointed out another correlary advantage of the dilution measure; namely, that it is desirable to dissolve the mass of exudate in a fluid of low density because exudate is more readily absorbed in solution of low density. Although no direct study has been reported on this mechanism in the peritoneum, it must remain as a theoretical factor possibly somewhat effective when any vehicle is used for the introduction of any substance employed to prevent adhesions. Even if this method were effective, its value must be slight on account of the practical difficulty in keeping large quantities of fluid in the peritoneal cavity during the period of exudation following injury.

Measures for Neutralizing the Prothrombin Factor.—Heparin is the only substance that has been proposed as an antiprothrombin.[7, 74, 80, 105, 108, 118] Since the majority of physiologists now believe that this drug acts mainly as an antithrombin, it will be discussed later.

Measures for Neutralizing the Calcium Factor.—In attacking the calcium factor in the peritoneal exudate, the calcium ions can theoretically be neutralized either by precipitating them with an oxalate solution or by binding them with a citrate solution.[7, 80]

Experimental (Table VII).—Pope[133] (1914) reported a series of rabbit experiments in which sodium citrate was employed, failing to record the number of animals in the experimental groups or in the control group. He observed that none of the experimental animals formed adhesions, while the control animals showed them in a "2 plus" degree. Sweet, Chaney, and Willson[163] (1915) unsuccessfully employed citrate solution against adhesion formation in a small series of dog experiments. Walker and Ferguson[168] (1916) reported several small series of uncontrolled rabbit experiments with sodium citrate; they believed that their results indicated some effectiveness of the drug. Kubota[87] (1922) published a small series of rabbit experiments employing 1 to 3 per cent sodium citrate in which both the experimental and control animals formed adhesions in 100 per cent of instances.

Clinical (Table VIII).—Surgeons in the past have occasionally commented upon the possible clinical value of using citrate or oxalate solutions intraperitoneally for adhesion prevention, but only Pope[134] (1916) undertook clinical investigation. He reported a large, uncontrolled series of pelvic laparotomies in which 2 per cent sodium citrate solution was employed for this purpose. A single administration of 120 c.c. was given intraperitoneally just before closure of the abdomen. Though Pope mentioned in his report that ten patients came to relaparotomy, no record was made as to whether or not adhesions were observed at subsequent operation.

TABLE VII

CITRATES (ANIMAL INVESTIGATIONS)

NAME (YR.)	CASES	ANIMALS		PRODUCT USED			TESTED AGAINST	ADHESIONS PRODUCED BY*	ADMINISTRATION OF SOLUTION (INTRA-PERITONEAL)				INTERVAL BEFORE POSTOPERATIVE EXAMINATION	NO. OF ANIMALS FORMING OR REFORMING ADHESIONS (%)
		SPECIES	NO.	NAME	STRENGTH	VEHICLE			HOW ADMINISTERED	NO. ADMINISTERED	WHEN ADMINISTERED	AMOUNT ADMINISTERED		
Pope (1914)	Experiment	Rabbits	N.R.†	Sodium citrate	1%	NaCl (normal)	Adhesion formation	(E)	N.R.	Single	Close of operation	15 c.c.	7 days	None
	Experiment	Rabbits	N.R.	Sodium citrate	2%	NaCl (4%)	Adhesion formation	(E)	N.R.	Single	Close of operation	15 c.c.	7 days	None
	Experiment	Rabbits	N.R.	Sodium citrate	2%	NaCl (3%)	Adhesion formation	(E)	N.R.	Single	Close of operation	15 c.c.	7 days	None
	Controls	Rabbits	N.R.	0	0	0	Adhesion formation	(E)	0	0	0	0	7 days	2 plus
Sweet, Chaney, and Willson (1915)	Experiment	Dogs	7	Sodium citrate	3%	N.R.	Adhesion formation	Anastomoses (SB)	Tube	Single	Close of operation	50 c.c.	7-14 days	100% in 5 survivals
	Controls	Dogs	2	0	0	0	Adhesion formation	Anastomoses (SB)	0	0	0	0	6-8 weeks	None

*A. Scarification of bowel. *B.* Chemical peritonitis, usually iodine. *C.* Combination of *A* and *B*. *D.* Donaldson's pledget technique. *E.* Scratching bowel. *F.* Perforation of appendix.

†*N.R.* No record.

Walker and Ferguson (1916)	Experiment	Rabbits	6	Sodium citrate	2%	NaCl (3%)	Adhesion formation	(E)	N.R.	Single	Close of operation	12 c.c.	4 days	4 (67%)
	Experiment	Rabbits	7	Sodium citrate	2%	NaCl (8%)	Adhesion formation	(E)	N.R.	Single	Close of operation	12 c.c.	4 days	5 (72%)
	Experiment	Rabbits	4	Sodium citrate	1%	NaCl (2%)	Adhesion formation	(E)	N.R.	Single	Close of operation	12 c.c.	4 days	3 (75%)
	Experiment	Rabbits	4	Sodium citrate	2%	NaCl (1%)	Adhesion formation	(E)	N.R.	Single	Close of operation	12 c.c.	4 days	4 (100%)
	Experiment	Rabbits	2	Sodium citrate	2%	NaCl (2%)	Adhesion formation	(E)	N.R.	Single	Close of operation	12 c.c.	4 days	2 (100%)
	Experiment	Rabbits	17	Sodium citrate	3%	NaCl (1%)	Adhesion formation	(E)	N.R.	Single	Close of operation	25 c.c.	4 days	5 (30%)
	Experiment	Rabbits	18	Sodium citrate	1-3%	Water	Adhesion re-formation	(G)	N.R.	Single	Close of operation	N.R.	N.R.	17 (95%)
	Controls	(None)												
Kubota (1922)	Experiment	Rabbits	3	Sodium citrate	1-3%	Water	Adhesion formation	(C)	N.R.	Single	Close of operation	5-100 c.c.	4-21 days	3 (100%)
	Controls	Rabbits	12	0	0	0	Adhesion formation	(C)	0	0	0	0	1-21 days	12 (100%)

TABLE VIII

CITRATES (CLINICAL INVESTIGATIONS)

NAME (YR.)	PRODUCT USED	TESTED AGAINST	CASES	FIRST OPERATION				ADHESION CHECK AT REOPERATION		ADHESION CHECK AT POST MORTEM		
				TYPE OPERATIONS	NO. CASES	NO. CASES WITH ADHESIONS (%)	HOW PRODUCT USED	NO. CASES	NO. CASES WITH ADHESIONS (%)	NO. DEATHS	NO. POST-MORTEM EXAMINATIONS	NO. CASES WITH ADHESIONS (%)
Pope (1916)	Sodium citrate 2%	Adhesion formation	Experiment	Major gynecologic and surgical operations	400	N.R.*	Up to 120 c.c. at close of operation	10	N.R.	N.R.	--	--
			Control	(None)								

*N.R. No record.

In summary, experimental attempts to neutralize calcium ions have offered contradictory and inconclusive results, and there is no clinical evidence of any value. Theoretically, much the same objections are present with citrate and oxalate solutions as have been repeatedly pointed out with other simple crystalloid solutions.

Measures for Neutralizing the Thrombokinase Factor.—Hirudin has been believed to exhibit both antithrombin and antikinase properties.[80, 125] Mellanby,[80, 107] however, more recently considers the antikinase effect its most important action.

Schmiedt about 1890 is credited by Vogel[167] and Jorpes[80] as the first physician to introduce hirudin solution into the abdominal cavities of animals as an antiadhesion measure. He was reported as having observed some inhibitory action against adhesion formation. The reports of no other studies on hirudin in the peritoneal cavity have been found. Purified heparin has supplanted hirudin in all recent work on anticoagulants.

Measures for Neutralizing the Fibrinogen Factor.—Around 1900, Vogel[167] unsuccessfully employed peptone solution against adhesions with the idea that it would prevent coagulation as an antifibrinogen. Recent investigations in peptone shock have shown a prolongation of the blood clotting time when peptone is administered in any fashion, due to an increased formation and liberation of heparin by the liver.[7, 80, 105, 175]

Hertzler[68, 69] (1904) reported attempting to neutralize the fibrinogen factor in the peritoneal exudate by giving phosphorus by mouth and peptone solution subcutaneously. The results were apparently inconclusive and the experiments were not further prosecuted.

The existence of an antifibrinogen has not been established and the approach has therefore only historical interest.

Measures for Neutralizing the Thrombin Factor.—Recently, the anticoagulant attack against peritoneal adhesion formation has been revived by Lehman and Boys[96, 97] employing heparin, an anticoagulant now considered to act as an antithrombin with possibly some antikinase and antiprothrombin side actions.[6, 7, 74, 80, 105, 108, 118]

Experimental.—A. Fischer,[48] Goerner,[58] and Zakrzenski[187] have observed that heparin employed in vitro inhibits cellular growth and tissue differentiation. Goerner believes that heparin prevented growth of tumor cells in tissue cultures by preventing fibrin deposition, the latter being necessary as a scaffolding over which the cells proliferate.

Miki and Satani[110] (1935) experimented with heparin in the peritoneal cavity of the rabbit, employing a crude product. They reported that after scarifying the peritoneum in the rabbits, the introduction of heparin-saline solution "considerably precluded" bowel agglutination. They found this solution much superior to sodium citrate.

Widstrom and Wilander[181] (1936) proposed the same principle for the prevention of pleural adhesions. After producing chemical pleuritis

in rabbits, purified heparin solution was injected into the pleural cavities at six, twenty-four, and forty-eight hours. These animals uniformly showed no fibrinous coatings or adhesions; whereas, the control animals showed fibrinous adhesions which were firmly organized within a few weeks.

Most of the animal experiments of Lehman and Boys[96, 97] deal with the prevention of the re-formation of divided intra-abdominal adhesions in the dog, but our preliminary studies deal with the initial prevention of the formation of peritoneal adhesions in the rabbit.

In 56 preliminary rabbit experiments[96] both mechanical damage to and bacterial contamination of the peritoneum were produced. In the experimental animals, heparin solution was introduced intra-abdominally before closure, and these injections were repeated by paracentesis once daily on the ensuing two postoperative days. The results indicated a striking difference in the number of adhesions formed between the control and experimental groups. In the mechanical trauma experiments all 26 control animals showed adhesion formation, but only 1 of 10 heparin animals presented any adhesions. In the contamination experiments none of the heparin-treated animals developed adhesions, while all of the controls formed them.

In dog experiments, designed to parallel the common surgical problem, the results again suggested considerable effectiveness of heparin in preventing adhesions. In the work already reported[96, 97] adhesions were caused by peritoneal contamination, but during the past year[99] a scarification technique has been employed satisfactorily. Six weeks after production of adhesions, the abdomen was reopened and adhesions were counted and divided. At this time, control and experimental groups were established. In the latter, heparin solution was injected intraperitoneally by paracentesis at the conclusion of the operation, and postoperatively in the same manner at varying intervals for the next two to four days. The final laparotomy for checking the results in both groups was performed four to six weeks later. The controls included animals receiving amniotic fluid, papain, normal saline solution, and no solution. In all of the control groups a greater number of adhesions re-formed than were divided. In contrast, the heparin-treated animals re-formed only about one-third as many adhesions as were divided. This difference has been approximately maintained throughout a large series of still unpublished observations, totaling around 300 experiments in dogs. Lehman and Boys also attempted to measure the effective dose in the dog, finding that heparin must be administered intraperitoneally for at least three days after adhesions are divided if the maximum effect is to be obtained. Repeated division of adhesions with subsequent heparinization will often completely abolish adhesions in dogs.[99] Owings and Hewitt[128] (1940), working with a small number of cats, report that the method seems to be effective.

Although heparin seems to have in animals a greater degree of success and more consistent results in the prevention of adhesions than any other substance previously studied, it presents one serious disadvantage; namely, the possibility of intraperitoneal hemorrhage. If the prevention of the coagulation of exudate is effective, the possible simultaneous prevention of the deposition of fibrin in the cut ends of blood vessels is an obvious danger. In earlier work, Lehman and Boys lost several animals from exsanguination. It was found, however, that this danger was minimal when particular care was taken with capillary hemostasis.

On the theoretical basis that fibrin might possibly not form in an exudate derived from heparinized blood, Lehman and Boys[97] performed a few dog experiments on the prevention of the re-formation of peritoneal adhesions by intravenous and subcutaneous administration of heparin. The experiments, being too few in number, and the results too inconclusive, have not been reported.

Clinical.—Lehman and Boys[98] have recently summarized 14 clinical cases of intraperitoneal heparinization for the prevention of the re-formation of divided adhesions (unpublished data). Seven of these patients were treated at the University of Virginia Hospital, and 7 at the hands of surgeons elsewhere. In most of the patients heparin was given immediately after operation and through an inlying catheter at twelve-hour intervals for six subsequent doses to a total of 400 mg. (40,000 units). Ten patients had a smooth postoperative course. One patient suffered a stormy course after the administration of a brand of heparin now known to be toxic. One patient died at the University of Virginia Hospital from intraperitoneal hemorrhage. This patient was badly chosen for use of the method in that operation was done about two weeks after a previous laparotomy for obstruction so that the peritoneum contained granulation tissue at the time heparin was introduced. In addition, this patient was inadequately followed postoperatively.

It is felt that this fatality presents no final contraindication to the clinical use of the method, but rather emphasizes its danger and the precautions that must attend its employment. These authors believe it is proper to use intraperitoneal heparin in the group of cases that have had previous obstructive episodes from adhesions provided no active granulation tissue is present and hemostasis is perfect. They stress the essential importance of extremely close postheparin observations for symptoms and signs of hemorrhage, and point out that the cessation of heparin administration together with adequate transfusions should theoretically prevent fatality from hemorrhage even though the latter should occur.

The report of these 14 cases includes detailed consideration of the clinical technique of intraperitoneal heparinization and postoperative care. No data are presented dealing with the effectiveness of the method in preventing adhesions in the human being.

In summary, extensive experimental evidence from one laboratory, supplemented by a small study from another laboratory, indicates that

the heparin attack against adhesions through the prevention of the coagulation of fibrin is promising, possibly more promising than any other method previously proposed. There is as yet no clinical evidence to this effect. Present clinical experience serves only to emphasize the care with which a potentially dangerous measure must be employed. The theoretical basis of possible effectiveness seems sound. The experimental observations must be further confirmed in other laboratories and tentative clinical experience must be much greater before intraperitoneal heparinization can be considered a standard procedure.

CONCLUSIONS

From this review it is apparent that up to the present time only one prophylaxis has been established against peritoneal adhesions; namely, the minimization at operation of all forms of peritoneal damage and the avoidance of intraperitoneal infection. Since these cannot be entirely prevented in practice, the need for supplementary prophylactic measures remains urgent.

The evidence presented from the literature suggests that the use of heparin at the present time is the most promising of such supplementary measures yet proposed. It seems to have a sound theoretical background and has presented consistent experimental results. In addition, it is the only substance proposed which is native to the body. Except for saline and glucose solutions, all other methods involve the use of substances foreign to the body. Heparin carries with it, however, the definite risk of hemorrhage.

The evidence for the effectiveness of various measures is conclusive in no instance. The reason for the failure to demonstrate effectiveness of any measure need not necessarily be ascribed to the assumption that the particular measure is ineffective. After nearly two years of continuous full-time investigation of one method in the laboratory, the author realizes the probable explanation for the previous inconclusive results; namely, insufficient laboratory study. Only in a very few other laboratories has study been continued for more than a few months.

In addition to further studies on heparin, certain other possibly effective antiadhesion methods need further critical evaluation. These include the other anticoagulants, the absorbable membranes, the sulfonamides alone and in conjunction with anticoagulants, and certain simple crystalloid solutions. In the study of the latter, the role of fluid bulk needs investigation. As a preliminary to such studies it is obvious that acceptable techniques must be perfected for standard adhesion production, and for objective measurement of results, techniques to be mastered only by long-time, extensive experience in the laboratory.

Finally, the evaluation of clinical results with any measure will demand a wider experience in cases that come to relaparotomy and to postmortem examination than has been reported with any method proposed. In individual instances a marked diminution in adhesions, when the abdomen is reopened later, may be of significant value. Conclusive evi-

dence, however, will depend upon the study and restudy of an enormous number of cases; such evidence will take years to accumulate. The standard adoption of any method of adhesion prevention, therefore, for the time being must depend upon laboratory evidence. Until extensive clinical data can be assembled, the application of a method to the patient can demonstrate only its safety or danger.

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